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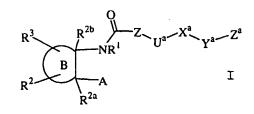
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(54) Title: CYCLIC β -AMINO ACID DERIVATIVES AS INHIBITORS OF MATRIX METALLOPROTEASES AND TNF- α



(57) Abstract: The present application describes novel cyclic β -amino acid derivatives of formula (I) or pharmaceutically acceptable salt forms thereof, wherein ring B is a 5-7 membered cyclic system containing from 0-2 heteroatoms selected from O, N, NR*, and S(O)_p, and 0-1 carbonyl groups and the other variables are defined in the present specification, which are useful as metalloprotease and as TNF- α inhibitors.

TITLE

CYCLIC β -AMINO ACID DERIVATIVES AS INHIBITORS OF MATRIX METALLOPROTEASES AND TNF- α

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FIELD OF THE INVENTION

This invention relates generally to novel cyclic $\beta-$ amino acid derivatives as matrix metalloproteases and TNF- $\!\alpha$ inhibitors, pharmaceutical compositions containing the same, and methods of using the same.

BACKGROUND OF THE INVENTION

There is now a body of evidence that metalloproteases (MP) are important in the uncontrolled breakdown of 15 connective tissue, including proteoglycan and collagen, leading to resorption of the extracellular matrix. This is a feature of many pathological conditions, such as rheumatoid and osteoarthritis, corneal, epidermal or gastric ulceration; tumor metastasis or invasion; periodontal 20 disease and bone disease. Normally these catabolic enzymes are tightly regulated at the level of their synthesis as well as at their level of extracellular activity through the action of specific inhibitors, such as alpha-2macroglobulins and TIMPs (tissue inhibitors of 25 metalloprotease), which form inactive complexes with the MP's.

Osteo- and Rheumatoid Arthritis (OA and RA respectively) are destructive diseases of articular cartilage characterized by localized erosion of the cartilage surface. Findings have shown that articular cartilage from the femoral heads of patients with OA, for example, had a reduced incorporation of radiolabeled sulfate over controls, suggesting that there must be an enhanced rate of cartilage degradation in OA (Mankin et al. J. Bone Joint Surg. 52A, 1970, 424-434). There are four classes of

protein degradative enzymes in mammalian cells: serine, cysteine, aspartic and metalloproteases. The available evidence supports that it is the metalloproteases which are responsible for the degradation of the extracellular matrix of articular cartilage in OA and RA. Increased activities of collagenases and stromelysin have been found in OA cartilage and the activity correlates with severity of the lesion (Mankin et al. Arthritis Rheum. 21, 1978, 761-766, Woessner et al. Arthritis Rheum. 26, 1983, 63-68 and Ibid.

10 27, 1984, 305-312). In addition, aggrecanase has been identified as providing the specific cleavage product of proteoglycan found in RA and OA patients (Lohmander L.S. et al. Arthritis Rheum. 36, 1993, 1214-22).

Therefore, metalloproteases (MP) have been implicated
as the key enzymes in the destruction of mammalian cartilage
and bone. It can be expected that the pathogenesis of such
diseases can be modified in a beneficial manner by the
administration of MP inhibitors, and many compounds have
been suggested for this purpose (see Wahl et al. Ann. Rep.
Med. Chem. 25, 175-184, AP, San Diego, 1990).

Tumor necrosis factor (TNF) is a cell-associated cytokine that is processed from a 26kd precursor form to a 17kd active form. TNF has been shown to be a primary mediator in humans and in animals, of inflammation, fever, and acute phase responses, similar to those observed during acute infection and shock. Excess TNF has been shown to be lethal. There is now considerable evidence that blocking the effects of TNF with specific antibodies can be beneficial in a variety of circumstances including autoimmune diseases such as rheumatoid arthritis (Feldman et al, Lancet, 1994, 344, 1105) and non-insulin dependent diabetes melitus. (Lohmander L.S. et al. Arthritis Rheum. 36, 1993, 1214-22) and Crohn's disease (MacDonald T. et al. Clin. Exp. Immunol. 81, 1990, 301).

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Compounds which inhibit the production of TNF are therefore of therapeutic importance for the treatment of inflammatory disorders. Recently, $TNF-\alpha$ converting enzyme (TACE), the enzyme responsible for TNF- α release from cells, were purified and sequenced (Black et al Nature 1997, 385, 729; Moss et al Nature 1997, 385, 733). This invention describes molecules that inhibit this enzyme and hence the secretion of active TNF- α from cells. These novel molecules provide a means of mechanism based therapeutic intervention for diseases including but not restricted to septic shock, haemodynamic shock, sepsis syndrome, post ischemic reperfusion injury, malaria, Crohn's disease, inflammatory bowel diseases, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancer, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, OA, RA, multiple sclerosis, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV and noninsulin dependent diabetes melitus.

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Since excessive TNF production has been noted in several disease conditions also characterized by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF production may also have a particular advantage in diseases where both mechanisms are involved.

EP 0,780,286 describes MMP inhibitors of formula A:

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wherein Y can be NHOH, R^1 and R^2 can combine to form a cycloalkyl or heterocyclo alkyl group, R^3 and R^4 can be a variety of groups including H, and R^5 can be substituted aryl.

WO 97/20824 depicts MMP inhibitors of formula B:

wherein ring V contains six atoms, Z is O or S, and Ar is an aryl or heteroaryl group. Ar is preferably a monocyclic aryl group with an optional para substituent or an unsubstituted monocyclic heteroaryl group.

EP 0,818,442 illustrates MMP inhibitors of formula C:

HOHN
$$(z)_q$$

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wherein Ar is optionally substituted phenyl or naphthyl, Z can be absent and X and Y can be a variety of substituents. Compounds of this sort are not considered to be part of the present invention.

The compounds of the present invention act as inhibitors of MPs, in particular TNF- α , MMPs, and/or aggrecanase. These novel molecules are provided as anti-inflammatory compounds and cartilage protecting therapeutics. The inhibition of aggrecanase, TNF-C, and other metalloproteases by molecules of the present invention indicates they are anti-inflammatory and should prevent the degradation of cartilage by these enzymes, thereby alleviating the pathological conditions of OA and RA.

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SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel cyclic hydroxamic acids useful as

metalloprotease inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to

10 provide a method for treating inflammatory disorders,
comprising: administering to a host, in need of such
treatment, a therapeutically effective amount of at least
one of the compounds of the present invention or a
pharmaceutically acceptable salt or prodrug form thereof.

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It is another object of the present invention to provide novel compounds of the present invention for use in therapy.

It is another object of the present invention to provide the use of novel compounds of the present invention for the manufacture of a medicament for the treatment of a condition or disease mediated by MMPs, TNF, aggrecanase, or a combination thereof.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula (I):

$$R^{3} \xrightarrow{R^{2b}} NR^{1} Z_{U^{a}} X^{a} Y^{a} Z^{a}$$

$$R^{2a} A$$

I

or pharmaceutically acceptable salt or prodrug forms

30 thereof, wherein A, B, R¹, R², R^{2a}, R^{2b}, and R³ are defined below, are effective metalloprotease inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in an embodiment, the present invention provides a novel compound of formula I:

$$R^{3} \xrightarrow{R^{2b}} NR^{1} Z_{U^{a}} X^{a}_{Y^{a}} Z^{a}$$

$$R^{2} \xrightarrow{R^{2a}} A$$

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

A is selected from $-COR^5$, $-CO_2H$, CH_2CO_2H , $-CO_2R^6$, -CONHOH, $-CONHOR^5$, $-CONHOR^6$, $-N(OH)COR^5$, -N(OH)CHO, -SH, $-CH_2SH$, $-S(O)(=NH)R^a$, $-SN_2H_2R^a$, $-PO(OH)_2$, and $-PO(OH)NHR^a$;

ring B is a 3-13 membered non-aromatic carbocyclic or
heterocyclic ring comprising: carbon atoms, 0-3

carbonyl groups, 0-4 double bonds, and from 0-2 ring
heteroatoms selected from O, N, NR², and S(O)_p, provided
that ring B contains other than a S-S, 0-O, or S-O
bond;

Z is absent or selected from a C₃₋₁₃ carbocycle substituted with 0-5 R^b and a 5-14 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p and substituted with 0-5 R^b;

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 X^a is absent or selected from C_{1-10} alkylene, C_{2-10} alkenylene, and C_{2-10} alkynylene;

 Y^a is absent or selected from O, NR^{a^1} , $S(O)_p$, and C(O);

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- Z^a is selected from H, a C_{3-13} carbocycle substituted with 0-5 R^c and a 5-14 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(0)_p$ and substituted with 0-5 R^c ;
- provided that Z, U^a , Y^a , and Z^a do not combine to form a N-N, N-O, O-N, O-O, $S(O)_p$ -O, O- $S(O)_p$ or $S(O)_p$ - $S(O)_p$ group;
- 15 R1 is selected from H, C1-4 alkyl, phenyl, and benzyl;
 - R^2 is selected from Q, Cl, F, C_{1-10} alkylene-Q substituted with 0-3 R^{b1} , C_{2-10} alkenylene-Q substituted with 0-3 R^{b1} , C_{2-10} alkynylene-Q substituted with 0-3 R^{b1} ,
- $(CR^{a}R^{a^{1}})_{r^{1}}O(CR^{a}R^{a^{1}})_{r^{-}}Q, (CR^{a}R^{a^{1}})_{r^{1}}NR^{a}(CR^{a}R^{a^{1}})_{r^{-}}Q,$ $(CR^{a}R^{a^{1}})_{r^{1}}C(0)(CR^{a}R^{a^{1}})_{r^{-}}Q, (CR^{a}R^{a^{1}})_{r^{1}}C(0)O(CR^{a}R^{a^{1}})_{r^{-}}Q,$ $(CR^{a}R^{a^{1}})_{r^{1}}C(0)O-C_{2-5} \text{ alkenylene, } (CR^{a}R^{a^{1}})_{r^{1}}C(0)O-C_{2-5}$ $alkynylene, (CR^{a}R^{a^{1}})_{r^{1}}OC(0)(CR^{a}R^{a^{1}})_{r^{-}}Q,$

 $(CR^{a}R^{a^{1}})_{r^{1}}C(0)NR^{a}R^{a^{1}}, (CR^{a}R^{a^{1}})_{r^{1}}C(0)NR^{a}(CR^{a}R^{a^{1}})_{r^{-0}},$

 $(CR^{a}R^{a^{1}})_{r^{1}}NR^{a}C(0)(CR^{a}R^{a^{1}})_{r^{-}}Q, (CR^{a}R^{a^{1}})_{r^{1}}OC(0)O(CR^{a}R^{a^{1}})_{r^{-}}Q,$ $(CR^{a}R^{a^{1}})_{r^{1}}OC(0)NR^{a}(CR^{a}R^{a^{1}})_{r^{-}}Q,$

 $(CR^aR^{a^1})_{r^1}NR^aC(0)O(CR^aR^{a^1})_{r^2}Q$

 $(CR^{a}R^{a^{1}})_{r^{1}}NR^{a}C(0)NR^{a}(CR^{a}R^{a^{1}})_{r}-Q$, $(CR^{a}R^{a^{1}})_{r^{1}}S(0)_{p}(CR^{a}R^{a^{1}})_{r}-Q$, $(CR^{a}R^{a^{1}})_{r^{1}}NR^{a}SO_{2}(CR^{a}R^{a^{1}})_{r}-Q$, and

30 $(CR^aR^{a^1})_r^1NR^aSO_2NR^a(CR^aR^{a^1})_r-Q;$

 R^{2a} is selected from H, C_{1-6} alkyl, OR^a , $NR^aR^{a^1}$, and $S(O)_pR^a$;

 R^{2b} is H or C_{1-6} alkyl;

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Q is selected from H, a C₃₋₁₃ carbocycle substituted with 0-5

R^d and a 5-14 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p and substituted with 0-5

R^d;

- 10 R³ is selected from Q¹, Cl, F, C₁₋₆ alkylene-Q¹, C₂₋₆ alkenylene-Q¹, C₂₋₆ alkynylene-Q¹, (CRaRa¹)_{r¹}O(CRaRa¹)_r-Q¹, (CRaRa¹)_{r¹}NRa (CRaRa¹)_r-Q¹, (CRaRa¹)_{r¹}NRaC(O)(CRaRa¹)_r-Q¹, (CRaRa¹)_{r¹}C(O)NRa(CRaRa¹)_r-Q¹, (CRaRa¹)_{r¹}C(O)(CRaRa¹)_r-Q¹, (CRaRa¹)_{r¹}C(O)(CRaRa¹)_r-Q¹, (CRaRa¹)_rC(O)(CRaRa¹)_r-Q¹, (CRaRa¹)_rC(O)_p(CRaRa¹)_r-Q¹, and (CRaRa¹)_{r¹}CO₂NRa(CRaRa¹)_r-Q¹;
- Q¹ is selected from H, phenyl substituted with 0-3 R^d,

 naphthyl substituted with 0-3 R^d and a 5-10 membered_

 heteroaryl comprising: carbon atoms and 1-4

 heteroatoms selected from the group consisting of N, O,

 and S(O)_p and substituted with 0-3 R^d;
 - R^a , at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl and benzyl;
 - R^{a^1} , at each occurrence, is independently selected from H and C_{1-4} alkyl;
- alternatively, R^a and R^{a¹} when attached to a nitrogen are
 taken together with the nitrogen to which they are
 attached to form a 5 or 6 membered ring comprising
 carbon atoms and from 0-1 additional heteroatoms
 selected from the group consisting of N, O, and S(O)_p;

 R^{a^2} , at each occurrence, is independently selected from C_{1-4} alkyl, phenyl and benzyl;

- 5 Rb, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, I, =0, -CN, NO_2 , $NR^aR^{a^1}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a^1}$, $R^aNC(O)NR^aR^{a^1}$, $OC(O)NR^aR^{a^1}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a^1}$, $NR^aS(O)_2R^{a^2}$, $NR^aS(O)_2NR^aR^{a^1}$, $OS(O)_2NR^aR^{a^1}$, $NR^aS(O)_2R^{a^2}$, $S(O)_pR^{a^2}$, CF_3 , and CF_2CF_3 ;
- R^{b1}, at each occurrence, is independently selected from OR^a,
 Cl, F, Br, I, =0, -CN, NO₂, and NR^aR^{a1};

- R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, I, =O, -CN, NO_2 , $NR^aR^{a^1}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a^1}$, $R^aNC(O)NR^aR^{a^1}$, $OC(O)NR^aR^{a^1}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a^1}$, $NR^aS(O)_2R^{a^2}$, $NR^aS(O)_2R^{a^2}$, $NR^aS(O)_2R^{a^2}$, $S(O)_pR^{a^2}$, CF_3 , CF_2CF_3 , C_{3-10} carbocycle substituted with O-3 R^{c1} and a S-14 membered heterocycle comprising: carbon atoms and S-14 heteroatoms selected from the group consisting of S, S, and S
- R^{c1} , at each occurrence, is independently selected from C_{1-6} 25 alkyl, OR^a , Cl, F, Br, I, =O, -CN, NO_2 , $NR^aR^{a^1}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a^1}$, $R^aNC(O)NR^aR^{a^1}$, $OC(O)NR^aR^{a^1}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a^1}$, $NR^aS(O)_2R^a^2$, $NR^aS(O)_2NR^aR^{a^1}$, $OS(O)_2NR^aR^{a^1}$, $NR^aS(O)_2R^a^2$, $S(O)_R^aR^a^2$, $OS(O)_R^aR^a^2$, $OS(O)_R^a$
- 30 R^d , at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, I, =O, -CN, NO_2 , $NR^aR^{a^1}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a^1}$, $R^aNC(O)NR^aR^{a^1}$, $OC(O)NR^aR^{a^1}$, $R^aNC(O)O$,

 $S(O)_2NR^aR^{a^1}$, $NR^aS(O)_2R^{a^2}$, $NR^aS(O)_2NR^aR^{a^1}$, $OS(O)_2NR^aR^{a^1}$, $NR^aS(O)_2R^{a^2}$, $S(O)_pR^{a^2}$, CF_3 , CF_2CF_3 , C_{3-10} carbocycle and a 5-14 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

 R^5 , at each occurrence, is selected from C_{1-10} alkyl substituted with 0-2 R^b , and C_{1-8} alkyl substituted with 0-2 R^e ;

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- R^e , at each occurrence, is selected from phenyl substituted with 0-2 R^b and biphenyl substituted with 0-2 R^b ;
- R⁶, at each occurrence, is selected from phenyl, naphthyl,

 C₁₋₁₀ alkyl-phenyl-C₁₋₆ alkyl-, C₃₋₁₁ cycloalkyl, C₁₋₆

 alkylcarbonyloxy-C₁₋₃ alkyl-, C₁₋₆ alkoxycarbonyloxy-C₁₋₃

 alkyl-, C₂₋₁₀ alkoxycarbonyl, C₃₋₆

 cycloalkylcarbonyloxy-C₁₋₃ alkyl-, C₃₋₆

 cycloalkoxycarbonyloxy-C₁₋₃ alkyl-, C₃₋₆

 cycloalkoxycarbonyl, phenoxycarbonyl,

 phenyloxycarbonyloxy-C₁₋₃ alkyl-, phenylcarbonyloxy-C₁₋₃

20 cycloalkoxycarbonyl, phenoxycarbonyl,
phenyloxycarbonyloxy-C₁₋₃ alkyl-, phenylcarbonyloxy-C₁₋₃
alkyl-, C₁₋₆ alkoxy-C₁₋₆ alkylcarbonyloxy-C₁₋₃ alkyl-,
[5-(C₁-C₅ alkyl)-1,3-dioxa-cyclopenten-2-one-yl]methyl,
[5-(R^a)-1,3-dioxa-cyclopenten-2-one-yl]methyl,

25 (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyl, $-C_{1-10}$ alkyl-NR⁷R^{7a}, $-CH(R^8)OC(=0)R^9$, and $-CH(R^8)OC(=0)OR^9$;

 R^7 is selected from H and C_{1-10} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl- C_{1-3} alkyl-, and phenyl- C_{1-6} alkyl-;

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 R^{7a} is selected from H and C_{1-10} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl- C_{1-3} alkyl-, and phenyl- C_{1-6} alkyl-;

 R^8 is selected from H and C_{1-4} linear alkyl;

 R^9 is selected from H, C_{1-8} alkyl substituted with 1-2 R^f , C_{3-8} cycloalkyl substituted with 1-2 R^f , and phenyl substituted with 0-2 R^b ;

 R^f , at each occurrence, is selected from C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{1-5} alkoxy, and phenyl substituted with 0-2 R^b ;

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- p, at each occurrence, is selected from 0, 1, and 2;
- r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and,

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 r^{1} , at each occurrence, is selected from 0, 1, 2, 3, and 4.

[2] In a preferred embodiment, the present invention provides a novel compound of formula II:

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or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

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A is selected from $-CO_2H$, CH_2CO_2H , -CONHOH, $-CONHOR^5$, $-CONHOR^6$, $-N(OH)COR^5$, -N(OH)CHO, -SH, and $-CH_2SH$;

ring B is a 4-7 membered non-aromatic carbocyclic or

heterocyclic ring comprising: carbon atoms, 0-1
carbonyl groups, 0-1 double bonds, and from 0-2 ring

heteroatoms selected from O, N, and NR², provided that ring B contains other than a O-O bond;

- Z is absent or selected from a C₃₋₁₁ carbocycle substituted
 with 0-4 R^b and a 5-11 membered heterocycle comprising:
 carbon atoms and 1-4 heteroatoms selected from the
 group consisting of N, O, and S(O)_p and substituted
 with 0-3 R^b;
- 10 Ua is absent or is selected from: O, NRa1, C(O), C(O)O, C(O)NRa1, NRa1C(O), S(O)D, and S(O)DNRa1;
 - X^a is absent or selected from C_{1-4} alkylene, C_{2-4} alkenylene, and C_{2-4} alkynylene;
 - Ya is absent or selected from O and NRa1;

- Z^a is selected from H, a C₃₋₁₀ carbocycle substituted with 0-5 R^c and a 5-10 membered heterocycle comprising:

 carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p and substituted with 0-5 R^c;
- provided that Z, U^a , Y^a , and Z^a do not combine to form a N-N, N-O, O-N, O-O, $S(O)_p$ -O, O- $S(O)_p$ or $S(O)_p$ -S(O)_p group;
 - R^1 is selected from H, C_{1-4} alkyl, phenyl, and benzyl;
- R² is selected from Q, C_{1-6} alkylene-Q, C_{2-6} alkenylene-Q, $C_{2-6} \text{ alkynylene-Q}, \quad (CR^aR^{a^1})_{r^1}O(CR^aR^{a^1})_{r^-}Q,$ $(CR^aR^{a^1})_{r^1}NR^a(CR^aR^{a^1})_{r^-}Q, \quad (CR^aR^{a^1})_{r^1}C(0)(CR^aR^{a^1})_{r^-}Q,$ $(CR^aR^{a^1})_{r^1}C(0)O(CR^aR^{a^1})_{r^-}Q, \quad (CR^aR^{a^1})_{r^0}C(0)NR^aR^{a^1},$

 $(CR^{a}R^{a^{1}})_{r^{1}}C(0)NR^{a}(CR^{a}R^{a^{1}})_{r}-Q, \quad (CR^{a}R^{a^{1}})_{r^{1}}S(0)_{p}(CR^{a}R^{a^{1}})_{r}-Q,$ and $(CR^{a}R^{a^{1}})_{r^{1}}SO_{2}NR^{a}(CR^{a}R^{a^{1}})_{r}-Q;$

- Q is selected from H, a C₃₋₆ carbocycle substituted with 0-5 R^d, and a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p and substituted with 0-5 R^d;
- 10 R^a , at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl and benzyl;

- R^{a^1} , at each occurrence, is independently selected from H and C_{1-4} alkyl;
- alternatively, Ra and Ral when attached to a nitrogen are taken together with the nitrogen to which they are attached to form a 5 or 6 membered ring comprising carbon atoms and from 0-1 additional heteroatoms selected from the group consisting of N, O, and S(O)p;
 - R^{a^2} , at each occurrence, is independently selected from C_{1-4} alkyl, phenyl and benzyl;
- 25 R^b , at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, =O, -CN, $NR^aR^{a^1}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a^1}$, $S(O)_2NR^aR^{a^1}$, $S(O)_pR^{a^2}$, and CF_3 ;
- R^c , at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, =0, -CN, $NR^aR^{a^1}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a^1}$, $S(O)_2NR^aR^{a^1}$, $S(O)_pR^{a^2}$, CF_3 , C_{3-6} carbocycle and a 5-6 membered heterocycle comprising: carbon

atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(0)_p$;

R^d, at each occurrence, is independently selected from C₁₋₆

alkyl, OR^a, Cl, F, Br, =0, -CN, NR^aR^{a¹}, C(0)R^a, C(0)OR^a,

C(0)NR^aR^{a¹}, S(0)₂NR^aR^{a¹}, S(0)_pR^{a²}, CF₃, C₃₋₆ carbocycle

and a 5-6 membered heterocycle comprising: carbon

atoms and 1-4 heteroatoms selected from the group

consisting of N, O, and S(O)_p;

- $R^5,$ at each occurrence, is selected from C_{1-6} alkyl substituted with 0-2 $R^b,$ and C_{1-4} alkyl substituted with 0-2 $R^e;$
- 15 Re, at each occurrence, is selected from phenyl substituted with 0-2 Rb and biphenyl substituted with 0-2 Rb;
- R⁶, at each occurrence, is selected from phenyl, naphthyl,

 C₁₋₁₀ alkyl-phenyl-C₁₋₆ alkyl-, C₃₋₁₁ cycloalkyl, C₁₋₆

 alkylcarbonyloxy-C₁₋₃ alkyl-, C₁₋₆ alkoxycarbonyloxy-C₁₋₃

 alkyl-, C₂₋₁₀ alkoxycarbonyl, C₃₋₆

 cycloalkylcarbonyloxy-C₁₋₃ alkyl-, C₃₋₆

 cycloalkoxycarbonyloxy-C₁₋₃ alkyl-, C₃₋₆

 cycloalkoxycarbonyl, phenoxycarbonyl,

 phenyloxycarbonyloxy-C₁₋₃ alkyl-, phenylcarbonyloxy-C₁₋₃

 alkyl-, C₁₋₆ alkoxy-C₁₋₆ alkylcarbonyloxy-C₁₋₃ alkyl-,

 [5-(C₁-C₅ alkyl)-1,3-dioxa-cyclopenten-2-one-yl]methyl,
- $[5-(R^a)-1,3-dioxa-cyclopenten-2-one-yl] methyl,$ $(5-aryl-1,3-dioxa-cyclopenten-2-one-yl) methyl, -C_{1-10}$ $alkyl-NR^7R^{7a}, -CH(R^8)OC(=0)R^9, and -CH(R^8)OC(=0)OR^9;$
 - R^7 is selected from H and C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl- C_{1-3} alkyl-, and phenyl- C_{1-6} alkyl-;

 R^{7a} is selected from H and C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl- C_{1-3} alkyl-, and phenyl- C_{1-6} alkyl-;

- 5 R8 is selected from H and C1-4 linear alkyl;
 - R^9 is selected from H, C_{1-6} alkyl substituted with 1-2 R^f , C_{3-6} cycloalkyl substituted with 1-2 R^f , and phenyl substituted with 0-2 R^b ;

Rf, at each occurrence, is selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-5} alkoxy, and phenyl substituted with 0-2 R^b ;

- 15 p, at each occurrence, is selected from 0, 1, and 2;
 - r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and,
- 20 r1, at each occurrence, is selected from 0, 1, 2, 3, and 4.
 - [3] In a more preferred embodiment, the present invention provides a novel compound of formula IIIa or IIIb:

IIIa · IIIb

- or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;
- 30 A is selected from -CO₂H, CH₂CO₂H, -CONHOH, -CONHOR⁵,
 -N(OH)CHO, and -N(OH)COR⁵;

Z is absent or selected from a C_{5-6} carbocycle substituted with 0-3 R^b and a 5-6 membered heteroaryl comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(0)_p$ and substituted with 0-3 R^b ;

 U^a is absent or is selected from: 0, NR^{a^1} , C(0), $C(0)NR^{a^1}$, $S(0)_p$, and $S(0)_pNR^{a^1}$;

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- X^a is absent or selected from C_{1-4} alkylene, C_{2-4} alkenylene, and C_{2-4} alkynylene
- Ya is absent or selected from O and NRa1;

15

- Z^a is selected from H, a C_{5-6} carbocycle substituted with 0-3 R^c and a 5-10 membered heteroaryl comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(0)_p$ and substituted with 0-3 R^c ;
- provided that Z, U^a , Y^a , and Z^a do not combine to form a N-N, N-O, O-N, O-O, $S(O)_p$ -O, O-S(O)_p or $S(O)_p$ -S(O)_p group;
- 25 R^1 is selected from H, C_{1-4} alkyl, phenyl, and benzyl;
- R² is selected from Q, C_{1-6} alkylene-Q, C_{2-6} alkenylene-Q, C_{2-6} alkynylene-Q, $(CR^aR^{a^1})_{r^1}C(0)(CR^aR^{a^1})_{r}-Q$, $(CR^aR^{a^1})_{r^1}C(0)O(CR^aR^{a^1})_{r}-Q$, $(CR^aR^{a^2})_{r^1}C(0)NR^aR^{a^1}$, $(CR^aR^a^2)_{r^1}C(0)NR^a(CR^aR^a^1)_{r}-Q$, and $(CR^aR^a^1)_{r^1}S(0)_{r^1}(CR^aR^a^1)_{r^2}Q$;

Q is selected from H, a C_{3-6} carbocycle substituted with 0-3 R^d and a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-3 R^d ;

 R^a , at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl and benzyl;

5

- 10 R^{a1} , at each occurrence, is independently selected from H and C_{1-4} alkyl;
 - R^{a^2} , at each occurrence, is independently selected from C_{1-4} alkyl, phenyl, and benzyl;
 - R^b , at each occurrence, is independently selected from C_{1-4} alkyl, OR^a , Cl, F, =0, $NR^aR^{a^1}$, $C(0)R^a$, $C(0)OR^a$, $C(0)NR^aR^{a^1}$, $S(0)_2NR^aR^{a^1}$, $S(0)_pR^{a^2}$, and CF_3 ;
- 20 R^c , at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, =O, $NR^aR^{a^1}$, $C(O)R^a$, $C(O)NR^aR^{a^1}$, $S(O)_2NR^aR^{a^1}$, $S(O)_pR^{a^2}$, and CF_3 ;
 - R^d , at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, =O, $NR^aR^{a^1}$, $C(O)R^a$, $C(O)NR^aR^{a^1}$, $S(O)_2NR^aR^{a^1}$, $S(O)_pR^{a^2}$, CF_3 , and phenyl;
 - R^5 , at each occurrence, is selected from C_{1-4} alkyl substituted with 0-2 R^b , and C_{1-4} alkyl substituted with 0-2 R^e ;
 - Re, at each occurrence, is selected from phenyl substituted with 0-2 Rb and biphenyl substituted with 0-2 Rb;

- p, at each occurrence, is selected from 0, 1, and 2;
- r, at each occurrence, is selected from 0, 1, 2, 3, and 4;
 - r¹, at each occurrence, is selected from 0, 1, 2, 3, and 4; and,

s and s^1 combine to total 2, 3, or 4.

10

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[4] In a further preferred embodiment, the present invention provides a novel compound of formula IVa or IVb:

$$R^{2}N \xrightarrow{S^{1}} NR^{1} \xrightarrow{N} OH$$

$$NR^{1} \xrightarrow{V} V^{2} Z^{2}$$

15

IVb

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

Z is absent or selected from phenyl substituted with 0-3 R^b and pyridyl substituted with 0-3 R^b;

Ua is absent or is 0;

25 Xa is absent or is CH2 or CH2CH2;

Ya is absent or is 0;

Z^a is selected from H, phenyl substituted with 0-3 R^c,

pyridyl substituted with 0-3 R^c, and quinolinyl

substituted with 0-3 R^c;

provided that Z, U^a , Y^a , and Z^a do not combine to form a N-N, N-O, O-N, or O-O group;

R¹ is selected from H, CH₃, and CH₂CH₃;

5

- R^2 is selected from Q, C_{1-6} alkylene-Q, C_{2-6} alkynylene-Q, $C(0)(CR^aR^{a^1})_r$ -Q, $C(0)(CR^aR^{a^1})_r$ -Q, $C(0)NR^a(CR^aR^{a^1})_r$ -Q, and $S(0)_p(CR^aR^{a^1})_r$ -Q;
- 10 Q is selected from H, cyclopropyl substituted with 0-1 R^d, cycloputyl substituted with 0-1 R^d, cyclopentyl substituted with 0-1 R^d, cyclohexyl substituted with 0-1 R^d, phenyl substituted with 0-2 R^d and a heteroaryl substituted with 0-3 R^d, wherein the heteroaryl is selected from pyridyl, quinolinyl, thiazolyl, furanyl, imidazolyl, and isoxazolyl;
 - Ra, at each occurrence, is independently selected from H, CH3, and CH2CH3;

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- ${\ensuremath{ ext{R}}^{a^1}},$ at each occurrence, is independently selected from H, ${\ensuremath{ ext{CH}}_3},$ and ${\ensuremath{ ext{CH}}_2\text{CH}_3};$
- R^{a^2} , at each occurrence, is independently selected from H, CH₃, and CH₂CH₃;
 - R^b , at each occurrence, is independently selected from C_{1-4} alkyl, OR^a , Cl, F, =0, $NR^aR^{a^1}$, $C(0)R^a$, $C(0)OR^a$, $C(0)NR^aR^{a^1}$, $S(0)_2NR^aR^{a^1}$, $S(0)_pR^{a^2}$, and CF_3 ;

30

 R^{c} , at each occurrence, is independently selected from C_{1-6} alkyl, OR^{a} , Cl, F, Br, =0, $NR^{a}R^{a^{1}}$, $C(0)R^{a}$, $C(0)NR^{a}R^{a^{1}}$, $S(0)_{2}NR^{a}R^{a^{1}}$, $S(0)_{5}R^{a^{2}}$, and CF_{3} ;

 R^d , at each occurrence, is independently selected from C_{1-6} —alkyl, OR^a , Cl, F, Br, =0, $NR^aR^{a^1}$, $C(O)R^a$, $C(O)NR^aR^{a^1}$, $S(O)_2NR^aR^{a^1}$, $S(O)_pR^{a^2}$, CF_3 and phenyl;

- p, at each occurrence, is selected from 0, 1, and 2;
- r, at each occurrence, is selected from 0, 1, 2, and 3;
- 10 r¹, at each occurrence, is selected from 0, 1, 2, and 3; and, s and s¹ combine to total 2, 3, or 4.
- 15 [5] In another more preferred embodiment, the present invention provides a novel compound of formula II, wherein;
- A is selected from $-CO_2H$, CH_2CO_2H , -CONHOH, $-CONHOR^5$, 20 -N(OH)CHO, and $-N(OH)COR^5$;
- ring B is a 4-7 membered non-aromatic carbocyclic or
 heterocyclic ring comprising: carbon atoms, 0-1
 carbonyl groups, 0-1 double bonds, and from 0-2 ring
 heteroatoms selected from O, N, and NR², provided that
 ring B contains other than a 0-0 bond;
- Z is absent or selected from a C_{5-6} carbocycle substituted with 0-3 R^b and a 5-6 membered heteroaryl comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(0)_p$ and substituted with 0-3 R^b ;

 U^a is absent or is selected from: 0, NR^{a^1} , C(0), $C(0)NR^{a^1}$, $S(0)_p$, and $S(0)_pNR^{a^1}$;

- X^a is absent or selected from C_{1-2} alkylene, C_{2-4} alkenylene, and C_{2-4} alkynylene
 - Ya is absent or selected from O and NRa1;
- Z^a is selected from H, a C₅₋₆ carbocycle substituted with 0-3

 R^c and a 5-10 membered heteroaryl comprising carbon

 atoms and from 1-4 heteroatoms selected from the group

 consisting of N, O, and S(O)_p and substituted with 0-3

 R^c;
- provided that Z, U^a , Y^a , and Z^a do not combine to form a N-N, N-O, O-N, O-O, $S(0)_p$ -O, $O-S(0)_p$ or $S(0)_p$ -S(O)_p group;
 - R^1 is selected from H, C_{1-4} alkyl, phenyl, and benzyl;
- 20 R^2 is $(CR^aR^{a^1})_{r^1}O(CR^aR^{a^1})_{r^2}Q$ or $(CR^aR^{a^1})_{r^1}NR^a(CR^aR^{a^1})_{r^2}Q$;
- Q is selected from H, a C₃₋₆ carbocycle substituted with 0-3

 R^d and a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p and substituted with 0-3

 R^d;
 - R^a , at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl and benzyl;

30

 \mathbb{R}^{a^1} , at each occurrence, is independently selected from H and \mathbb{C}_{1-4} alkyl;

 R^{a^2} , at each occurrence, is independently selected from C_{1-4} alkyl, phenyl and benzyl;

- R^b , at each occurrence, is independently selected from C_{1-4} alkyl, OR^a , C1, F, =0, $NR^aR^{a^1}$, $C(0)R^a$, $C(0)OR^a$, $C(0)NR^aR^{a^1}$, $S(0)_2NR^aR^{a^1}$, $S(0)_DR^{a^2}$, and CF_3 ;
- R^{c} , at each occurrence, is independently selected from C_{1-6} alkyl, OR^{a} , Cl, F, Br, =O, $NR^{a}R^{a^{1}}$, $C(O)R^{a}$, $C(O)NR^{a}R^{a^{1}}$, $S(O)_{D}R^{a}R^{a^{2}}$, and CF_{3} ;
 - R^d , at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, =O, $NR^aR^{a^1}$, $C(O)R^a$, $C(O)NR^aR^{a^1}$, $S(O)_2NR^aR^{a^1}$, $S(O)_pR^{a^2}$, CF_3 and phenyl;

 R^5 , at each occurrence, is selected from C_{1-4} alkyl substituted with 0-2 R^b , and C_{1-4} alkyl substituted with 0-2 R^e ;

15

- 20 R^e , at each occurrence, is selected from phenyl substituted with 0-2 R^b and biphenyl substituted with 0-2 R^b ;
 - p, at each occurrence, is selected from 0, 1, and 2;
- 25 r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and,
 - r^1 , at each occurrence, is selected from 0, 1, 2, 3, and 4.
 - [6] In another further preferred embodiment, the present invention provides a novel compound of formula II, wherein;

A is -CONHOH;

ring B is a 5-6 membered non-aromatic carbocyclic or
heterocyclic ring comprising: carbon atoms, 0-1
carbonyl groups, 0-1 double bonds, and from 0-2 ring
heteroatoms selected from O, N, and NR², provided that
ring B contains other than a 0-0 bond;

Z is absent or selected from phenyl substituted with 0-3 R^b
and pyridyl substituted with 0-3 R^b;

Ua is absent or is 0;

Xa is absent or is CH2 or CH2CH2;

15

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Ya is absent or is 0;

 Z^a is selected from H, phenyl substituted with 0-3 R^c, pyridyl substituted with 0-3 R^c, and quinolinyl substituted with 0-3 R^c;

provided that Z, U^a , Y^a , and Z^a do not combine to form a N-N, N-O, O-N, or O-O group;

25 R¹ is selected from H, CH₃, and CH₂CH₃;

 R^2 is $(CR^aR^{a^1})_{r^1}O(CR^aR^{a^1})_{r^2}Q$ or $(CR^aR^{a^1})_{r^1}NR^a(CR^aR^{a^1})_{r^2}Q$;

Q is selected from H, cyclopropyl substituted with 0-1 R^d,

cyclobutyl substituted with 0-1 R^d, cyclopentyl

substituted with 0-1 R^d, cyclohexyl substituted with

0-1 R^d, phenyl substituted with 0-2 R^d, and a heteroaryl

substituted with 0-3 R^d, wherein the heteroaryl is

selected from pyridyl, quinolinyl, thiazolyl, furanyl, imidazolyl, and isoxazolyl;

- Ra, at each occurrence, is independently selected from H, CH3, and CH2CH3;
 - R^{a^1} , at each occurrence, is independently selected from H, CH_3 , and CH_2CH_3 ;
- 10 R^{a^2} , at each occurrence, is independently selected from H, CH_3 , and CH_2CH_3 ;
- R^b , at each occurrence, is independently selected from C_{1-4} alkyl, OR^a , Cl, F, =0, $NR^aR^{a^1}$, $C(0)R^a$, $C(0)OR^a$, $C(0)NR^aR^{a^1}$, $S(0)_2NR^aR^{a^1}$, $S(0)_pR^{a^2}$, and CF_3 ;
 - R^{C} , at each occurrence, is independently selected from C_{1-6} alkyl, OR^{a} , Cl, F, Br, =0, $NR^{a}R^{a^{1}}$, $C(0)R^{a}$, $C(0)NR^{a}R^{a^{1}}$, $S(0)_{2}NR^{a}R^{a^{1}}$, $S(0)_{p}R^{a^{2}}$, and CF_{3} ;
 - R^d , at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, =0, $NR^aR^{a^1}$, $C(O)R^a$, $C(O)NR^aR^{a^1}$, $S(O)_2NR^aR^{a^1}$, $S(O)_pR^{a^2}$, CF_3 and phenyl;
- 25 p, at each occurrence, is selected from 0, 1, and 2;

- r, at each occurrence, is selected from 0, 1, 2, and 3; and,
- r^1 , at each occurrence, is selected from 0, 1, 2, and 3.
 - [7] In another preferred embodiment, the present invention provides a compound selected from the group:

	(trifluoromethyl)[1,1'-biphenyl]-4-carboxamide -
5	N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-4-[2-(trifluoromethyl)phenoxy]benzamide
	N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-4-(3-methyl-2-pyridinyl)benzamide
10	N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}[1,1'-biphenyl]-4-carboxamide
15	N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-4-phenoxybenzamide
	4-(benzyloxy)-N-{(1R,2S)-2- [(hydroxyamino)carbonyl]cyclopentyl}benzamide
20	N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-2'- methoxy[1,1'-biphenyl]-4-carboxamide
	N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-2'- methyl[1,1'-biphenyl]-4-carboxamide
25	N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-4-(2-methoxyphenoxy)benzamide
	$N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-4-(2-methylphenoxy)benzamide$
	N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-4-(3-methylphenoxy)benzamide
35	4-(5,8-dihydro-4-quinolinyl)-N-{(1R,2S)-2- [(hydroxyamino)carbonyl]cyclopentyl}benzamide
	N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-3',5' dimethyl[1,1'-biphenyl]-4-carboxamide
40	$N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-6-(2-methylphenyl)nicotinamide$
1 5	N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-6-(2-methoxyphenyl)nicotinamide
	(3S,4S)-N-hydroxy-1-isopropyl-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
50	(3S,4S)-1-(2,2-dimethylpropanoyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide

. 5	quinolinyl)methoxy]benzoyl}amino)-1-(methylsulfonyl)-3 pyrrolidinecarboxamide
3	<pre>(3S, 4S) -N-hydroxy-1-methyl-4-({4-[(2-methyl-4- quinolinyl)methoxy]benzoyl}amino)-3- pyrrolidinecarboxamide</pre>
10	<pre>tert-butyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2- methyl-4-quinolinyl)methoxy]benzoyl}amino)-1- pyrrolidinecarboxylate</pre>
15	<pre>(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4- quinolinyl)methoxy]benzoyl}amino)-3- pyrrolidinecarboxamide</pre>
20	<pre>tert-butyl 4-[cis-3-[(hydroxyamino)carbonyl]-4-({4-[(2- methyl-4- quinolinyl)methoxy]benzoyl}amino)pyrrolidinyl]-1- piperidinecarboxylate</pre>
25	<pre>cis-N-hydroxy-4-({4-[(2-methyl-4-</pre>
30	<pre>cis-1-[3-[(1,1-dimethylethoxy)carbonyl]pyrollidinyl]-N- hydroxy-3-[[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-4- pyrollidinecarboxamide</pre>
35	<pre>cis-N-hydroxy-1-[3-pyrollidinyl]-3-[[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-4- pyrollidinecarboxamide</pre>
	<pre>tert-butyl (3R,4R)-3-[(hydroxyamino)carbonyl]-4-({4-[(2- methyl-4-quinolinyl)methoxy]benzoyl}amino)-1- pyrrolidinecarboxylate</pre>
40	<pre>tert-butyl (3S,4R)-3-[(hydroxyamino)carbonyl]-4-({4-[(2- methyl-4-quinolinyl)methoxy]benzoyl}amino)-1- pyrrolidinecarboxylate</pre>
4 5	(3S,4R)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
50	<pre>tert-butyl (3R,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2- methyl-4-quinolinyl)methoxy]benzoyl}amino)-1- pyrrolidinecarboxylate</pre>

	<pre>(3R, 4S) -N-hydroxy-4-({4-{(2-methy1-4- quinolinyl)methoxy]benzoyl}amino)-3- pyrrolidinecarboxamide</pre>
5	N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-4-(4-pyridinyl)benzamide
10	(3S, 4S)-1-(1,1-dimethyl-2-propynyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
15	(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-(2-propynyl)-3-pyrrolidinecarboxamide
	<pre>(3S, 4S) -1-allyl-N-hydroxy-4-({4-[(2-methyl-4- quinolinyl)methoxy]benzoyl}amino)-3- pyrrolidinecarboxamide</pre>
20	<pre>(3S, 4S) -N-hydroxy-4-({4-[(2-methyl-4- quinolinyl)methoxy]benzoyl}amino)-1-propyl-3- pyrrolidinecarboxamide</pre>
25	(3S,4S)-N-hydroxy-1-(2-methyl-2-propenyl)-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
30	(3S,4S)-1-(1,1=dimethyl-2-propenyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
35	(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-tert-pentyl-3-pyrrolidinecarboxamide
,,	(3S,4S)-N-hydroxy-1-isopentyl-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
40	(3S, 4S) -N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-neopentyl-3-pyrrolidinecarboxamide
15	<pre>(3S, 4S) -1-butyl-N-hydroxy-4-({4-[(2-methyl-4- quinolinyl)methoxy]benzoyl}amino)-3- pyrrolidinecarboxamide</pre>
50	(3S, 4S)-1-(3-butenyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide

	quinolinyl)methoxy]benzoyl}amino)-3- pyrrolidinecarboxamide
5	(3S,4S)-1-(2-furylmethyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
10	(3S,4S)-N-hydroxy-1-[(5-methyl-2-furyl)methyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
15	(3R,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)tetrahydro-3-furancarboxamide
20	(3S,4R)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methöxy]benzoyl}amino)tetrahydro-3-furancarboxamide
20	(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-(1,3-thiazol-2-ylmethyl)-3-pyrrolidinecarboxamide
25	<pre>(3S,4S)-1-acetyl-N-hydroxy-4-({4-[(2-methyl-4- quinolinyl)methoxy]benzoyl}amino)-3- pyrrolidinecarboxamide</pre>
30	(3S,4S)-N-hydroxy-1-isobutyryl-4-({4-[(2-methyl-4-quinolinyl-)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
35	(3S,4S)-N-hydroxy-1-(3-methylbutanoyl)-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
40	<pre>(3S,4S)-1-(cyclopropylcarbonyl)-N-hydroxy-4-({4-[(2-methyl- 4-quinolinyl)methoxy]benzoyl}amino)-3- pyrrolidinecarboxamide</pre>
± 0	<pre>(3S,4S)-1-(cyclobutylcarbonyl)-N-hydroxy-4-({4-[(2-methyl-4</pre>
45	<pre>(3S,4S)-N-hydroxy-1-(methoxyacetyl)-4-({4-[(2-methyl-4- quinolinyl)methoxy]benzoyl}amino)-3- pyrrolidinecarboxamide</pre>
50	(3S,4S)-1-(2-furoyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pvrrolidinecarboxamide

	(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4- :: quinolinyl)methoxy]benzoyl}amino)-1-(2-thienylcarbonyl)-3-pyrrolidinecarboxamide
5	<pre>(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4- quinolinyl)methoxy]benzoyl}amino)-1-propionyl-3- pyrrolidinecarboxamide</pre>
10	(3R,4S)-4-{[4-(2-butynyloxy)benzoyl]amino}-N-hydroxy-tetrahydro-3-furancarboxamide
	N-{(1R,2S)-2-[(hydroxyamino)carbonyl]-4-oxocyclopentyl}-4- [(2-methyl-4-quinolinyl)methoxy]benzamide
15	N-{(1R,2S,4R)-4-hydroxy-2- [(hydroxyamino)carbonyl]cyclopentyl}-4-[(2-methyl-4- quinolinyl)methoxy]benzamide
20	N-{(1R,2S,4S)-4-hydroxy-2- [(hydroxyamino)carbonyl]cyclopentyl}-4-[(2-methyl-4- quinolinyl)methoxy]benzamide
25	(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-tetrahydro-2H-pyran-4-yl-3-pyrrolidinecarboxamide
30	<pre>methyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl- 4-quinolinyl)methoxy]benzoyl}amino)-1- pyrrolidinecarboxylate</pre>
30	ethyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-pyrrolidinecarboxylate
35	<pre>propyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl- 4-quinolinyl)methoxy]benzoyl}amino)-1- pyrrolidinecarboxylate</pre>
40	<pre>allyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4- quinolinyl)methoxy]benzoyl}amino)-1- pyrrolidinecarboxylate</pre>
45	<pre>isopropyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2- methyl-4-quinolinyl)methoxy]benzoyl}amino)-1- pyrrolidinecarboxylate</pre>
50	<pre>2-propynyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2- methyl-4-quinolinyl)methoxy]benzoyl}amino)-1- pyrrolidinecarboxylate</pre>
JU	2-butynyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-pyrrolidinecarboxylate

5	<pre>methyl-4-quinolinyl)methoxylbenzoyl}amino)-1- pyrrolidinecarboxylate</pre>
5	<pre>benzyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl- 4-quinolinyl)methoxy]benzoyl}amino)-1- pyrrolidinecarboxylate</pre>
10	N-{(1R,2S)-4-(dimethylamino)-2- [(hydroxyamino)carbonyl]cyclopentyl}-4-[(2-methyl-4- quinolinyl)methoxy]benzamide
15	(3S, 4S)-4-{[4-(2-butynyloxy)benzoyl]amino}-N-hydroxy-1-isopropyl-3-pyrrolidinecarboxamide
20	<pre>N-{(1R,2S)-4,4-difluoro-2- [(hydroxyamino)carbonyl]cyclopentyl}-4-[(2-methyl-4- quinolinyl)methoxy]benzamide</pre>
20	(3S, 4S) -N-hydroxy-1-isopropyl-4-{[4-(2-methylphenoxy)benzoyl]amino}-3-pyrrolidinecarboxamide
25	<pre>cis-N-hydroxy-2-[[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-1- cyclopentanecarboxamide</pre>
30	<pre>trans-N-hydroxy-2-[[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-1- cyclopentanecarboxamide</pre>
35	<pre>(1S, 2R) -N-hydroxy-2-[[[4-[(2-methyl-4-</pre>
35	<pre>(1R,2S) -N-hydroxy-2-[[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-1- cyclopentanecarboxamide</pre>
40	<pre>cis-N-hydroxy-2-[[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-1- cyclohexanecarboxamide</pre>
45	<pre>trans-N-hydroxy-2-[[[4-[(2-methyl-4-</pre>
50	trans-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-pyrrolidinecarboxamide

	<pre>trans-N-hydroxy-3-[[[4-[(2-methyl-4-</pre>
5	<pre>cis-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-3-[[[4-</pre>
10	<pre>cis-N-hydroxy-3-[[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-4- pyrrolidinecarboxamide</pre>
15	(3S,4R)-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-4- [[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-3- piperidinecarboxamide
20	(3S,4S)-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-4- [[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-3- piperidinecarboxamide
25	(3S,4S)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
30	(3S,4R)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
	(3S, 4R)-1-[(butoxy)carbonyl]-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
35	(3S, 4R)-N-hydroxy-1-[[(1-methylethyl)oxy]carbonyl]-4-[[[4- [(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]- 3-piperidinecarboxamide
40	(3S, 4R)-N-hydroxy-1-(methylsulfonyl)-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
45	(3S, 4R) -N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(phenylsulfonyl)-3-piperidinecarboxamide
50	(3S,4R)-1-acetyl-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide

	quinolinyl)methoxy]phenyl]carbonyl]amino]-3- piperidinecarboxamide
5	(3S, 4R)-1-(2,2-dimethylpripionyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
10	(3S,4R)-1-(3,3-dimethylbutanoyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
15	(3S, 4R) -N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(4-morpholinecarbonyl)-3-piperidinecarboxamide
20	(3S, 4R)-1-(dimethylcarbamyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
20	(3S,4R)-N-hydroxy-1-methyl-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
25	(3S,4R)-1-ethyl-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
30	(3S,4R)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-propyl-3-piperidinecarboxamide
35	(3S,4R)-N-hydroxy-1-(1-methylethyl)-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
	(3S,4R)-1-(cyclopropylmethyl)-N-hydroxy-4-[[[4-[(2-methyl-4 quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
40	(3S,4R)-1-(2,2-dimethylpropyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
45	(3S, 4R)-1-benzyl-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
50	(3S, 4R)-1-(2-thiazolylmethyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide

	<pre>(3S, 4S) -1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-3- [[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-4- piperidinecarboxamide</pre>
5	(3R,4S)-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-3- [[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-4- piperidinecarboxamide
10	(3R,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
15	(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
20	(3S,4S)-N-hydroxy-1-[[(2-methylpropyl)oxy]carbonyl]-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino4-piperidinecarboxamide
25	(3S,4S)-N-hydroxy-1-(methoxycarbonyl)-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
30	(3S,4S)-N-hydroxy-1-[(1-methylethoxy)carbonyl]-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
30	(3S,4S)-N-hydroxy-1-(methylsulfonyl)-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
35	(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(phenylsulfonyl)-4-piperidinecarboxamide
40	(3S,4S)-1-(3,3-dimethylbutanoyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
45	(3S,4S)-1-(2,2-dimethylpropionyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
50	(3S,4S)-1-benzoyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide

	(3S, 4S)-1-[(pyridin-3-yl)carbonyl]-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
5	(3S, 4S) -N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(2-thiophenecarbonyl)-4-piperidinecarboxamide
10	(3S, 4S)-1-(dimethylcarbamyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
15	(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(4-morpholinecarbonyl)-4-piperidinecarboxamide
20	(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-[[2-(2-thienyl)ethyl]carbamyl]-4-piperidinecarboxamide
20	(3S,4S)-1-[(1,1-dimethylethyl)carbamyl]-N-hydroxy-3-[[[4- [(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino] 4-piperidinecarboxamide
25	(3S,4S)-N-hydroxy-1-methyl-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
30	(3S,4S)-1-ethyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
35	(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-propyl-4-piperidinecarboxamide
	(3S,4S)-N-hydroxy-1-(1-methylethyl)-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
40	(3S,4S)-1-cyclobutyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
45	(3S,4S)-1-butyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
50	(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(2-methylproxyl)-4-piperidinogarboyamide

	quinolinyl)methoxy]phenyl]carbonyl]amino]-4- piperidinecarboxamide
5	(3S,4S)-1-(2,2-dimethylpropyl)-N-hydroxy-3-[[[4-[(2-methyl 4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
10	(3S,4S)-1-cyclopentyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
15	(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(4-tetrahydropyranyl)-4-piperidinecarboxamide
20	(3S,4S)-1-benzyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
20	(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(2-thiazolylmethyl)-4-piperidinecarboxamide
25	(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(4-pyridinylmethyl)-4-piperidinecarboxamide
30	(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(2-pyridinylmethyl)-4-piperidinecarboxamide
35	(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(3-pyridinylmethyl)-4-piperidinecarboxamide
	(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(trans-3-phenyl-2-propenyl)-4-piperidinecarboxamide
40	(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-phenyl-4-piperidinecarboxamide
45	(3R,4S)-1-(2,2-dimethylpropionyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
50	(3R, 4S) -N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-methyl-4-

5	quinolinyl)methoxy]phenyl]carbonyl]amino]-4- piperidinecarboxamide
Э	(3S,4S)-1-hexyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
10	(3S,4S)-1-(2-fluoroethyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
15	(3S,4S)-1-(2,2-difluoroethyl)-N-hydroxy-3-[[[4-[(2-methyl-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
20	(3S,4S)-N-hydroxy-1-(1-methylpropyl)-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
25	(3S,4S)-1-(1-ethylpropyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
23	(3S,4S)-1-[1-[[(1,1-dimethylethyl)oxy]carbonyl]-4- tetrahydropiperidinyl]-N-hydroxy-3-[[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-4- piperidinecarboxamide
30	(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(4-tetrahydropiperidinyl)-4-piperidinecarboxamide
35	(3S, 4S)-1-[1-[[(1,1-dimethylethyl)oxy]carbonyl]-3- tetrahydropyrrolidinyl]-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4- piperidinecarboxamide
40	(3S, 4S) -N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(3-tetrahydropyrrolidinyl)-4-piperidinecarboxamide
45	(3S,4S)-1-(1,1-dimethyl-2-propynyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
50	(3S, 4S) -N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(3-thiophenylmethyl)-4-piperidinecarboxamide

	(3S,4S)-N-hydroxy-1-(1-methylethyl)-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-oxo-4-piperidinecarboxamide
5	(3S, 4S)-N-hydroxy-1-(1-methylethyl)-3-[[[4-[(2-methyl-1-oxo-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
10	(3S,4S)-N-hydroxy-1-(1-methylethyl)-3-[[[4-[(2-methyl-1-oxo-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-oxo-4-piperidinecarboxamide
15	(3S, 4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-[2-(4-morpholinyl)-2-oxoethyl]-4-piperidinecarboxamide
20	(3S,4S)-1-[2-(N,N-dimethylamino)-2-oxoethyl]-N-hydroxy-3- [[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-4- piperidinecarboxamide
25	(3S,4S)-1-(t-butylsulfonyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
	(3S,4S)-1-(t-butylsulfonyl)-N-hydroxy-3-[[[4-[(2-methyl-1-oxo-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
30	(3S,4S)-1-(benzenesulfonyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
35	(3S,4S)-1-(t-butylsulfinyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
40	(3S,4S)-N-hydroxy-1-(2-hydroxylethyl)-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
45	<pre>(3S,4S)-1-[2-[[[(1,1- dimethylethyl)oxy]carbonyl]amino]ethyl]-N-hydroxy-3- [[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-4- piperidinecarboxamide</pre>
50	(3S, 4S)-1-(2-aminoethyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide

(3S, 4S) - 1 - [2 - (N, N-dimethylamino) ethyl] - N-hydroxy - 3 - [[4 - [(2 - (N, N-dimethylamino) ethyl]] - N-hydroxy - 3 - [[4 - (N, N-dimethylamino) ethylamino) ethylamino emethyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide 5 (3S, 4S) - 1 - [(2S) - 2 - aminopropyl] - N - hydroxy - 3 - [[4 - (2 - methyl - me4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide (3S, 4S) - 1 - [(2R) - 2 - amino - 3 - hydroxypropy 1] - N - hydroxy - 3 - [[[4 - amino - 3 - hydroxymosy 1] - N - hydroxy - 3 - [[[4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - 3 - [[[4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - 3 - [[[4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - 3 - [[[4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - 3 - [[4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - 3 - [[4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - 3 - [[4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - 3 - [[4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - 3 - [[4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - 3 - [[4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - 3 - [[4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - 3 - [[4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - 3 - [[4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - 3 - [4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - [4 - amino - 3 - hydroxymosy 1] - N - hydroxymosy - [410 [(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-[[(2R)-2-15 pyrrolidinyl]methyl]-4-piperidinecarboxamide (3S, 4R) - N - hydroxy - 1 - (2 - hydroxylethyl) - 4 - [[[4 - [(2 - methyl) - 4 - [(3S - methyl) - 4 - (3S - methyl)]]]quinolinyl)methoxy]phenyl]carbonyl]amino]-3piperidinecarboxamide 20 (3S, 4R) - 1 - (2-aminoethyl) - N-hydroxy - 4 - [[4-[4-methyl] - 4-aminoethyl] - N-hydroxy - 4 - [4-[4-methyl] - 4-aminoethyll - 4-aminoethyquinolinyl)methoxy]phenyl]carbonyl]amino]-3piperidinecarboxamide 25 (3S, 4R)-1-cyclobutyl-N-hydroxy-4-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-3piperidinecarboxamide 30 quinolinyl)methoxy|benzoyl}amino)tetrahydro-2H-pyran-3carboxamide $(3S, 4S) - 1 - tert - butyl - N - hydroxy - 3 - ({4 - [(2 - methyl - 4 - 1)]})$ quinolinyl)methoxy]benzoyl}amino)-4-35 piperidinecarboxamide tert-butyl 2-[(3S, 4S)-4-[(hydroxyamino)carbonyl]-3-({4-[(2-

40

2-[(3S,4S)-4-[(hydroxyamino)carbonyl]-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)piperidinyl]-2-methylpropanoic acid

2-methylpropanoate

methyl-4-quinolinyl)methoxy]benzoyl)amino)piperidinyl]-

45 methyl 2-[(3S,4S)-4-[(hydroxyamino)carbonyl]-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)piperidinyl]-2-methylpropanoate

	<pre>(35,45)-N-nydroxy-3-({4-[(2-methy1-4- quinolinyl)methoxy]benzoyl}amino)-1-[2-(4-morpholinyl)- 2-oxoethyl]-4-piperidinecarboxamide</pre>
5	(3S,4S)-1-[2-(dimethylamino)-2-oxoethyl]-N-hydroxy-3-({4- [(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4- piperidinecarboxamide
10	(3S,4S)-1-(1,1-dimethyl-2-propenyl)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4-piperidinecarboxamide
15	(3S,4S)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-tert-pentyl-4-piperidinecarboxamide
00	(3S,4S)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-(2-propynyl)-4-piperidinecarboxamide
20	(3S,4S)-1-allyl-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4-piperidinecarboxamide
25	(3S,4S)-N-hydroxy-1-(1-methyl-2-propynyl)-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4-piperidinecarboxamide
30	(3S,4S)-N-hydroxy-1-(1-methyl-2-propenyl)-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4-piperidinecarboxamide
35	<pre>N-{(1R,2S)-4,5-dihydroxy-2- [(hydroxyamino)carbonyl]cyclohexyl}-4-[(2-methyl-4- quinolinyl)methoxy]benzamide</pre>
	(5S)-N-hydroxy-5-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-2-oxo-4-piperidinecarboxamide
40	(3S,4S)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-2-oxo-4-piperidinecarboxamide
45	(3S, 4S) -3-{[4-(2-butynyloxy)benzoyl]amino}-N-hydroxy-1-

 $(3S, 4S) - 3 - \{ [4 - (2 - butynyloxy) benzoyl] amino \} - N - hydroxy - 4 - butynyloxy benzoyl] amino \} - N - hydroxy - 4 - butynyloxy benzoyl] amino } - N - hydroxy - 4 - butynyloxy benzoyl] amino } - N - hydroxy - 4 - butynyloxy benzoyl] amino } - N - hydroxy - 4 - butynyloxy benzoyl] amino } - N - hydroxy - 4 - butynyloxy benzoyl] amino } - N - hydroxy - 4 - butynyloxy benzoyl] amino } - N - hydroxy - 4 - butynyloxy benzoyl] amino } - N - hydroxy - 4 - butynyloxy benzoyl] amino } - N - hydroxy - 4 - butynyloxy benzoyl] amino } - N - hydroxy - 4 - butynyloxy benzoyl] amino } - N - hydroxy - 4 - butynyloxy benzoyl] amino } - N - hydroxy - 4 - butynyloxy benzoyl] amino } - N - hydroxy - 4 - butynyloxy benzoyl] amino } - N - hydroxy - 4 - butynyloxy benzoyl] amino } - N - hydroxy - 4 - butynyloxy benzoyl benzo$ piperidinecarboxamide 5 tert-butyl $(3S, 4S)-4-[(hydroxyamino)carbonyl]-3-({4-[(2$ methyl-3-pyridinyl)methoxy]benzoyl}amino)-1piperidinecarboxylate $(3S, 4S) - N - hydroxy - 3 - (\{4 - [(2 - methyl - 3 - 1)]\})$ 10 pyridinyl)methoxy|benzoyl}amino)-4piperidinecarboxamide tert-butyl $(3S, 4S) - 3 - (\{4 - [(2, 5$ dimethylbenzyl) oxy]benzovl}amino) -4-15 [(hydroxyamino)carbonyl]-1-piperidinecarboxylate $(3S, 4S) - 3 - (\{4 - [(2, 5 - dimethylbenzyl) oxy] benzoyl\}amino) - N - (3S, 4S) - 3 - (\{4 - [(2, 5 - dimethylbenzyl) oxy] benzoyl\}amino) - N - (3S, 4S) - 3 - (\{4 - [(2, 5 - dimethylbenzyl) oxy] benzoyl) amino) - N - (3S, 4S) - ($ hydroxy-4-piperidinecarboxamide 20 (cis, cis) - 3 - Amino - 2 - [[[4 - [(2 - methyl - 4 - [(3 - methylquinolinyl) methoxy] phenyl] carbonyl] amino] - (Nhydroxy) cyclohexylcarboxamide (cis, cis) -3-Methylamino-2-[[[4-[(2-methyl-4-25 quinolinyl)methoxy]phenyl]carbonyl]amino]-(Nhydroxy) cyclohexylcarboxamide (cis, cis) -3-Dimethylmino-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(N-30 hydroxy) cyclohexylcarboxamide (cis, trans) -3-Amino-2-[[[4-[(2-methyl-4quinolinyl) methoxy | phenyl | carbonyl | amino | -1-(Nhydroxy) cyclohexylcarboxamide 35 (cis, trans)-3-Dimethylmino-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-(Nhydroxy) cyclohexylcarboxamide 40 (cis, trans) - 3 - (1-Methyl-1-ethylmino) - 2 - [[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-(Nhydroxy) cyclohexylcarboxamide (cis, trans) -3-Methylamino-2-[[[4-[(2-methyl-4-45 quinolinyl)methoxy]phenyl]carbonyl]amino]-(Nhydroxy) cyclohexylcarboxamide

	quinolinyl)methoxy]phenyl]carbonyl]amino]-(N- hydroxy)cyclohexylcarboxamide
5	N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-{[(2-methyl-4-quinolinyl)methyl]amino}benzamide
10	N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-{methyl[(2-methyl-4-quinolinyl)methyl]amino}benzamide
	N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-(3-phenyl-4,5-dihydro-5-isoxazolyl)benzamide
15	N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[3-(4-pyridinyl)-4,5-dihydro-5-isoxazolyl]benzamide
	<pre>N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[3-(3-pyridinyl)-4,5-dihydro-5-isoxazolyl]benzamide</pre>
20	<pre>N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[3-(2-pyridinyl)-4,5-dihydro-5-isoxazolyl]benzamide</pre>
25	N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[3-(4-quinolinyl)-4,5-dihydro-5-isoxazolyl]benzamide
	4-[3-(2,6-Dimethyl-4-pyridinyl)-4,5-dihydro-5-isoxazolyl]-N- {cis-2-[(hydroxyamino)carbonyl]cyclopentyl}benzamide
30	N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-3-methoxy-4-[3-(4-pyridinyl)-4,5-dihydro-5-isoxazolyl]benzamide
	3-Hydroxy-N-{cis-2-[(hydroxyamino)carbonyl]cyclopentyl}-4- [3-(4-pyridinyl)-4,5-dihydro-5-isoxazolyl]benzamide
35	N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[5-(2-pyridinyl)-4,5-dihydro-3-isoxazolyl]benzamide
40	N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[5-(4-pyridinyl)-4,5-dihydro-3-isoxazolyl]benzamide
¥ U	N-{4-[(hydroxyamino)carbonyl]-3-pyrrolidinyl}-1-[(2-methyl-4-quinolinyl)methyl]-1H-indole-5-carboxamide
4 5	<pre>N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-1-[(2-methyl-4- quinolinyl)methyl]-1H-indole-5-carboxamide</pre>
	N-hydroxy-3-({6-[(2-methyl-4-quinolinyl)methoxy]-1-naphthoyl}amino)-4-piperidinecarboxamide
50	N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-6-[(2-methyl-4-quinolinyl)methoxy]-1-naphthamide

	N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-6-[(2-methyl-4-quinolinyl)methoxy]-2-naphthamide
5	<pre>N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-6-[(2-methyl-4- quinolinyl)methoxy]-1,2,3,4-tetrahydro-1- isoquinolinecarboxamide</pre>
10	N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-1-[(2-methyl-4-quinolinyl)methyl]-1H-benzimidazole-5-carboxamide
	<pre>N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-1-[(2-methyl-4- quinolinyl)methyl]-1H-indole-4-carboxamide</pre>
15	<pre>(±)-cis-N-hydroxy-2-[[4-[(2-methyl-4- quinolinyl)methoxy]benzoyl]amino]-1- cycloheptanecarboxamide</pre>
20	<pre>(±)-trans-N-hydroxy-2-[[4-[(2-methyl-4- quinolinyl)methoxy]benzoyl]amino]-1- cycloheptanecarboxamide</pre>
25	(4S,5R)-N-hydroxy-5-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-2-oxohexahydro-1H-azepine-4-carboxamide
30	(3S,4S)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-7-oxohexahydro-1H-azepine-4-carboxamide
30	(3S,4R)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-7-oxohexahydro-1H-azepine-3-carboxamide
35	(4S,5R)-N-hydroxy-5-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-7-oxohexahydro-1H-azepine-4-carboxamide
40	(2S,3R)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-2-pyrrolidinecarboxamide
45	(2R,3R)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-2-pyrrolidinecarboxamide, and
50	<pre>tert-butyl (2S,3R)-2-[(hydroxyamino)carbonyl]-3-({4-[(2- methyl-4-quinolinyl)methoxy]benzoyl}amino)-1- pyrrolidinecarboxylate</pre>
-	or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

10 In another embodiment, the present invention provides a novel method for treating or preventing an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method of treating a condition or disease mediated by MMPs, TNF, aggrecanase, or a combination thereof in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

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In another-embodiment, the present invention provides a novel method of treating, wherein the disease or condition is referred to as acute infection, acute phase response, age related macular degeneration, alcoholism, anorexia, asthma, autoimmune disease, autoimmune hepatitis, Bechet's disease, cachexia, calcium pyrophosphate dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary disease, coagulation, congestive heart failure, corneal ulceration, Crohn's

disease, enteropathic arthropathy, Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid withdrawal syndrome, gout, graft versus host disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation, intermittent hydrarthrosis, Lyme disease, meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease, periodontitis, polymyositis/dermatomyositis, post-ischaemic reperfusion injury, post-radiation asthenia, psoriasis, psoriatic arthritis, pydoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and tumor invasion by secondary metastases, spondylitis, stroke, systemic lupus erythematosus, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis.

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In another embodiment, the present invention provides novel compounds of the present invention for use in therapy.

In another embodiment, the present invention provides the use of novel compounds of the present invention for the manufacture of a medicament for the treatment of a condition or disease mediated by MMPs, TNF, aggrecanase, or a combination thereof.

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DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically

active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Geometric isomers of double bonds such as olefins and C=N double bonds can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention.

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The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =0), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. When a ring system (e.g., carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double bond be part (i.e., within) of the ring.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e.g., Rb) occurs more than one time
in any constituent or formula for a compound, its definition

at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R⁶, then said group may optionally be substituted with up to two R⁶ groups and R⁶ at each occurrence is selected independently from the definition of R⁶. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond

connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic 20 hydrocarbon groups having the specified number of carbon atoms. C_{1-10} alkyl (or alkylene), is intended to include C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , and C_{10} alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, 25 n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example -CvFw where v=1 to 3 and w=1 to (2v+1)). Examples of haloalkyl 30 include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-10} alkoxy, is intended to include C_1 , C_2 , C_3 , C_4 , 35 C₅, C₆, C₇, C₈, C₉, and C₁₀ alkoxy groups. Examples of

alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. C_{3-7} cycloalkyl, is intended to include C3, C4, C5, C6, and C7 cycloalkyl groups. "Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl. 10 C_{2-10} alkenyl (or alkenylene), is intended to include C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , and C_{10} alkenyl groups. "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable - 15 point along the chain, such as ethynyl and propynyl. C_{2-10} alkynyl (or alkynylene), is intended to include C2, C3, C4, C_5 , C_6 , C_7 , C_8 , C_9 , and C_{10} alkynyl groups.

"Halo" or "halogen" as used herein refers to fluoro,
20 chloro, bromo, and iodo; and "counterion" is used to
represent a small, negatively charged species such as
chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-membered

25 monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or

13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

30 cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl.

As used herein, the term "heterocycle" or "heterocyclic 35 group" is intended to mean a stable 5, 6, or 7-membered

monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The nitrogen atom may be substituted or unsubstituted (i.e., -N 10 or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting 15 compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the 20 heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and 1, 2, 3, or 4 heterotams 25 independently selected from the group consisting of N, O and It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl,

benzothiofuranyl, benzothiophenyl, benzoxazolyl,
benzthiazolyl, benztriazolyl, benztetrazolyl,
benzisoxazolyl, benzisothiazolyl, benzimidazolinyl,
carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl,
chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl,

furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1Hindazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3Hindolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, 10 piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, 15 pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 20 thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4triazolyl, and xanthenyl. Also included are fused ring and 25 spiro compounds containing, for example, the above heterocycles.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; and alkali or organic salts of acidic residues such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium 10 salts of the parent compound formed, for example, from nontoxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic.

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The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable 35 qualities of pharmaceuticals (e.g., solubility,

bioavailability, manufacturing, etc...) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers which release an active parent drug of the present invention in vivo when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention. --

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"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective to inhibit a desired metalloprotease in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, Adv. Enzyme Regul. 22:27-55 (1984), occurs when the effect (in this case, inhibition of the desired target) of the compounds when administered in combination is greater

than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antiviral effect, or some other beneficial effect of the combination compared with the individual components.

SYNTHESIS

10 The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

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The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including. choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and work up procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction

conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

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A variety of compounds of formula (I) wherein A is hydroxamic acid group are prepared from the corresponding esters via several routes known in the literature (Scheme 1). The methyl ester of 1 ($R^{11}=Me$) is directly converted to hydroxamic acid 2 by treatment with hydroxylamine under basic conditions such as KOH or NaOMe in solvents such as methanol. The methyl ester of 1 (R^{11} =Me) can also be converted to 0-benzyl protected hydroxamic acid with 0benzylhydroxylamine under similar conditions or using Weinreb's trimethylalluminum conditions (Levin, J. I.; Turos, E.; Weinreb, S. M. Syn. Commun. 1982, 12, 989) or Roskamp's bis[bis(trimethylsilyl)amido]tin reagent (Wang, W.-B.; Roskamp, E. J. J. Org. Chem. 1992, 57, 6101). The benzyl ether is removed by methods well known in the literature such as hydrogenation using palladium on barium sulfate in hydrogen, to give compound 2. Alternatively, 2 can be prepared through the carboxylic intermediate 3. Carboxylic acid 3 is converted to 2 via coupling with hydroxylamine, or 0-benzylhydroxylamine followed by deprotection.

Scheme 1

The β -amino acid moiety in formula (I) can be synthesized following a variety of literature routes as reviewed in "Enantioselective Synthesis of β -Amino Acids" (E. Juaristi, Ed. Wiley-VCH, 1997). One representative approach using Davies protocol is summarized in Scheme 2 (J. Chem. Soc. Perkin Trans I, 1994, 1411). Michael addition of lithium amide 5 to 4 gives cis product 6. The stereochemical configuration of 6 is governed by the chirality of 5. Debenzylation of 6 provides cis- β -amino acid 7. The trans- β -amino acid 9 can be prepared by epimerization of 6 followed by de-benzylation. Since both amine enantiomers of 5 are commercially available, this approach provides ready access to both cis and trans isomers (7 and 9), as well as their antipodes.

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Scheme 2

5 Alternatively, these β -amino acids can be prepared from the corresponding dicarboxylate derivatives (Scheme 3). The dicarboxylate derivatives can be de-symmetrized through enzymatic resolution (for an example with lipase, see Gais, H.-J. et al, J. Am. Chem. Soc. 1989, 54, 5115), or through 10 chemical resolution (for an example with TADOLates, see Seebach, D. et al, Angew Chem Int. Ed. Engl. 1995, 34, 2395). The optically pure mono-ester 11 is converted to Cbz protected β-amino acid ester 12 through Curtius rearrangement (for a related example, see Kobayashi, S. et 15 al, Tetrahedron Lett. 1984, 25, 2557). Removal of Cbz protecting group provides cis amino acid ester 13. The corresponding trans analogue of 13 can be prepared from the ester of trans di-carboxylic acid of 10 following same sequence.

Scheme 3

5 A series of compounds of formula (I) wherein ring B is pyrrolidine are prepared following the sequence outlined in Scheme 4. Pyrrolidine 15 is prepared following a dipolar addition procedure documented in the literature (Joucla, M.; Mortier, J., J. Chem. Commun. 1985, 1566). Protecting group 10 manipulations and Curtius rearrangement (for a related example, see Kobayashi, S. et al, Tetrahedron Lett. 1984, 25, 2557) give intermediate 17. Hydrogenolysis gives amino acid ester 18. 18 is coupled with acid 20 to provide 21 with R¹ as H. To prepare analogues of **21** when R¹ is not a hydrogen, 18 is first converted to 19 by alkylation or 15 reductive amination, then coupled with 20. The pyrrolidine nitrogen in 21 is unmasked and functionalized to various tertiary amines, amides, carbamides, ureas, sulfonamides and sulfonyl ureas following procedures well known in the 20 literature. Ester 23 is converted to hydroxamic acid following sequence outlined in Scheme 1. Following the same sequence, the cis isomer of 23 can be prepared using benzyl methyl maleate as the starting material.

Scheme 4

A series of compounds of formula (I) wherein ring B is piperidine are prepared following the sequence outlined in Scheme 5. The β-amino acid moiety is prepared by reduction of enamine 27. Optically pure α-methylbenzylamine (26) is used to induce diastereoselectivity in the reduction (Cimarelli, C. et. al, J. Org. Chem. 1996, 61, 5557). Hydrogenolysis gives amino acid ester 29. 29 is coupled with acid 20 to provide 31 with R¹ as H. To prepare analogues of 31 when R¹ is not a hydrogen, 29 is first converted to 30 by alkylation or reductive amination, then coupled with 20. The

piperidine nitrogen in 31 is unmasked and functionalized to various tertiary amines, amides, carbamides, ureas, sulfonamides and sulfonyl ureas following procedures well known in the literature. Ester 33 is converted to hydroxamic acid following sequence outlined in Scheme 1. Regio-isomers of 33 with piperidine nitrogen transposed to other positions are prepared following a similar sequence. The antipode of 33 can be prepared using the S enantiomer of 26. The transisomer of 33 is prepared by epimerization of 31 or 33 under basic conditions (e.g., DBU, PhMe, at reflux).

Scheme 5

A series of compounds of formula (I) wherein ring B is piperidine and R^{2a} is hydroxy are prepared following the sequence outlined in Scheme 6. Ketone 34 is converted to enol triflate 35 following McMurry triflimide conditions (McMurry, J. E.; Scott, W. J. Tetrahedron Lett. 1983, 24, 979). Palladium-catalyzed carbonylation in methanol provides methyl ester 36. Epoxidation, epoxide opening with NaN3 and hydrogenation give intermediate 39 with amino and ester groups in cis relationship. The isomer with trans stereochemistry (43) is prepared using Sharpless asymmetric 10 aminohydroxylation and subsequent removal of Cbz group (Li, G.; Angert, H. H.; Sharpless, K. B. Angew. Chem. Int. Ed. Engl. 1996, 35, 2813). Coupling of 39 and 43 with acid 20 provides 40 and 44, respectively. Esters 40 and 44 are 15 converted to hydroxamic acids following sequence outlined in Scheme 1.

Scheme 6

A series of compounds of formula (I) wherein A is Nformylhydroxylamino group are prepared following the
sequence outlined in Scheme 7. Starting from trans-hydroxy
ester 45, Wenreib or Roskamp amide formation with 0-tbutylhydroxylamine gives 46 (Levin, J. I.; Turos, E.;
Weinreb, S. M. Syn. Commun. 1982, 12, 989 and Wang, W.-B.;

Roskamp, E. J. J. Org. Chem. 1992, 57, 6101). β-Lactam is formed under Mitsunobu conditions (Mitsunobu, O. Synthesis, 1981, 1). Opening of lactam 47 with methylamine followed by N-formylation provide 49. The N-methyl amide moiety of 49 is converted to carboxylic acid by nitrosation with N204 or NaNO2, and hydrolysis with LiOOH (Evans, D. A.; Carter, P. H.; Dinsmore, C. J.; Barrow, J. C.; Katz, J. L.; Kung, D. W. Tetrahedron Lett. 1997, 38, 4535). Acid 50 is converted to 53 as described previously. Acid hydrolysis of t-Butyl group in 53 completes the synthesis.

Scheme 7

A series of compounds of formula (I) wherein A is mercaptomethyl group are prepared following the sequence outlined in Scheme 8. Saponification and hydroboration of 55 give alcohol 57. Mitsunobu reaction with thioacetic acid followed by lithium hydroxide hydrolysis provides the desired thiol 59.

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Scheme 8

A variety of compounds of formula (I) wherein Z-U^a-X^a-Y^a-Z^a is a functionalized phenyl group can be prepared by methods described in Scheme 9. Intermediate 60, available from schemes described previously, is converted to phenol 61 by hydrogenolysis. Phenol 61 is used as common intermediates for structure diversification. Reaction of 61 with R¹⁰-X provides 62, an alternative is the reaction of 61 with R¹⁰-OH under Mitsunobu conditions to produce 62. R¹⁰ can be appended directly to the aromatic ring by converting 61 to an aryl triflate then reaction with an organometallic in the presence of a palladium (0) catalyst to give 63. 61 can also be reacted with acyl halides or isocyanates to afford 66. Biaryl ethers 65 can be produced by treatment of 61 with aryl boronic acids in the presence of a copper catalyst.

Esters 62-63 and 65-66 are converted to the hydroxamic acids following the sequences outlined in Scheme 1.

Scheme 9

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Compounds of formula 76 can be prepared starting from the commercially available 3-hydroxy-2-nitrobenzoic acid 67 (Scheme 10). Conversion of the carboxylic acid to an ester such as an ethyl ester 68 can be accomplished by refluxing in EtOH/benzene in the presence of sulfuric acid. Ester 68 can be reduced to a saturated cyclohexyl ring 69 by

hydrogenation in acidic aqueous solution using a catalyst such as PtO₂. Coupling of 69 with a benzoic acid derivative 70 using a coupling agent such as BOP produces the amide derivative 71 as the major diastereomer with a cis, cisstereochemistry. The hydroxyl group of 71 can be oxidized using an oxidizing agent such as the Dess-Martin periodinane to give a ketone derivative 72. Reductive amination of 72 with ammonium acetate or a primary amine using a reducing agent such as Na(OAc)₃BH affords the amino derivative 73. After Boc protection at the amino using di-tert-butyl-dicarbonate, saponification of the ethyl ester 74 at an elevated temperature using a base such as KOH in MeOH/H₂O followed by coupling of the resulting carboxylic acid with hydroxylamine hydrochloride using a coupling agent such as BOP produces the hydroxamic acid 75. Removal of the Boc

group using an acid such TFA/CH2Cl2 or 4 N HCl in dioxane

affords the final compounds of formula 76.

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Compounds of formula **78** can be obtained by reductive amination of the intermediate **73** with an aldehyde using a reducing agent such as Na(OAc)₃BH followed by conversion of the ethyl ester to a hydroxamate as shown in Scheme 11.

Scheme 11

Compounds of formula 80 can be obtained by reductive

amination of the intermediate 72 with a cycloamine such as
azetidine, pyrrolidine, piperidine or morpholine using a
reducing agent such as Na(OAc)₃BH followed by conversion of
the ethyl ester to a hydroxamate as shown in Scheme 12.

10 Scheme 12

Compound of formula 89 can be synthesized starting from the intermediate 69 which is coupled with 4-benzyloxybenzoic acid 81 using a coupling agent such as BOP, producing 82 as the major diastereomer with a cis, cis-stereochemistry

(Scheme 13). The hydroxyl group can be converted to a sulfonate such as a mesylate 83. Displacement of 83 with sodium azide produces the azido derivative 84 which is subjected to a hydrogenolysis using a catalyst such as Pd-C to give the primary amine 85. Mono Boc protection at the amino group is accomplished by reaction of 85 with di-tert-butyl-dicarbonate in THF/H₂O using a mixed base such as NaOH/NaHCO₃. Alkylation of 86 with 4-chloromethyl-2-methylquinoline using a base such as potassium carbonate in acetone at reflux affords the intermediate 87. Following saponification using a base such as KOH in MeOH/H₂O at an elevated temperature, the resulting carboxylic acid 88 is coupled with hydroxylamine hydrochloride using a coupling agent such as BOP. Removal of the Boc group using an acid such as TFA/CH₂Cl₂ produces the final compound 89.

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Scheme 13

Compounds of formula 92 can be prepared starting from
the intermediate 87 (Scheme 14). Saponification using a base
such as KOH in MeOH at an elevated temperature followed by
deprotection of the Boc group using an acid such as TFA in
CH₂Cl₂ produces the amino-carboxylic acid intermediate 90.
Reductive amination of 90 with a ketone using a reducing
agent such as Na(OAc)₃BH produces the secondary amine 91. The
hydroxamic acids of formula 92 can be obtained by coupling
the carboxylic acid with hydroxylamine hydrochloride using a
coupling agent such as BOP.

Scheme 14

Compounds of formula **95** can be obtained by reductive amination of the intermediate **90** with an aldehyde using a reducing agent such as Na(OAc)₃BH followed by conversion of the carboxylic acid to a hydroxamic acid as shown in Scheme 15.

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Compounds of formula 103 can be prepared starting from the intermediate 85 (Scheme 16). The mono-benzylated amino derivative 97 can be obtained by reductive amination of the

intermediate **85** with excess benzaldehyde using a reducing agent such as Na(OAc)₃BH followed by hydrogenation under atmospheric pressure using a catalyst such as Pd-C. Further alkylation at the benzylamino group by reductive amination with an aldehyde using a reducing agent such as Na(OAc)₃BH produces the tertiary amino derivative **98**. After removal of the benzyl group by hydrogenation, the secondary amine is protected by reaction with di-tert-butyl-dicarbonate.

Alkylation of the phenol derivative **100** with 4-chloromethyl-2-methylquinoline is followed by saponification of the ethyl ester using a base such as KOH in MeOH at reflux. Conversion of the carboxylic acid to a hydroxamic acid followed by acid deprotection of the Boc group affords compounds of formula **103**.

Compounds of formula 108 can be prepared starting from
the intermediate 83 (Scheme 17). Displacement of 83 with
ArOH produces the aryl ether 104. After removal of the
benzyl group by hydrogenation using a catalyst such as Pd-C,
the phenol moiety is alkylated with 4-chloromethyl-2methylquinoline. Saponification of the ethyl ester using a
base such as KOH in MeOH at reflux followed by coupling of
the resulting carboxylic acid with hydroxylamine
hydrochloride using a coupling agent such as BOP affords
compounds of formula 108.

108

5 The 3-hydroxyl analog of formula 110 can be prepared starting from the intermediate 71. Saponification using a base such as LiOH followed by coupling the resulting carboxylic acid with hydroxylamine hydrochloride using a coupling agent such as BOP provides the the final product with a cis, cis-stereochemistry.

Scheme 18

The cis-trans-diastereomeric analog of 110 can be prepared starting from the same intermediate 71. Inversion of the chirality at the 3-hydroxyl position can be accomplished by a Mitsunobu reaction with 4-nitrobenzoic acid. Hydrolysis using a base such as KOH removes the 4-nitrobenzoyl moiety and saponifies the ethyl ester. Coupling of the resulting carboxylic acid with hydroxylamine hydrochloride using a coupling agent such as BOP provides compound of formula 112.

Scheme 19

A series of compound of formula (I) where ring B is tetrahydropyran are prepared following the sequence outlined in Scheme 20. Treatment of the enolate of tetrahydropyranone 113 with Mander's reagent provides β-keto ester 114. Condensation of 114 with amine 115 gives enamine 10 116. Reduction of 116 with sodium (triacetoxy)borohydride proceeds stereoselectively to give desired amine 117. Hydrogenolysis and coupling with acid 20 provides ester 119. Ester 119 is converted to hydroxamic acid following sequence outline in Scheme 1.

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Scheme 20

Compounds of formula (I) wherein ring B is a tetrahydrofuran are prepared as outlined in Schemes 21 and 22. Michael addition of the sodium salt of methyl glycolate 120 to methyl acrylate and concomitant Dieckman cyclization provides the keto-ester 121. Enamine formation with (R)-α-10 methylbenzyl amine 115 and diastereoselective reduction gives 123. Hydrogenolysis gives the amino acid ester 124. 124 is coupled to acid 20 and converted to the hydroxamate 126.

Scheme 21

An alternative preparation (Scheme 22) of the amino acid ester 124 begins with the intermediate 121. Enamine formation with NH₄OAc and acetylation gives 128. Asymmetric hydrogenation using a chiral rhodium catalyst (*J. Am. Chem. Soc.* 1995, 117, 9375) and de-acetylation would yield 124 that could be converted similarly to hydroxamate 126.

Scheme 22

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Another procedure for the synthesis of cyclic ß-amino acids useful for the preparation of compounds of formula I uses the well documented [2+2] cycloaddition of chlorosulfonylisocyanate with olefins (Scheme 23, Dhar, D.N.; Murthy, K.S.K. Synthesis 1986, 437-449). When 130 is reacted with chlorosulfonylisocyanate the resulting ß-lactam intermediate 131 can be opened to afford cyclic ß-amino acids using a variety of conditions, but most conveniently with chlorotrimethylsilane/methanol. The methyl ester 13 can then be converted to compounds of formula I followed our usual procedure of attaching carboxcylic acid 20 to provide 132 then hydroxamic acid 133 is formed by our standard conditions. The trans ß-amino acids 134 are available by equilibration of cis amide ester 132 under basic conditions.

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Scheme 23

An alternative synthesis of 133 begins with formation of benzyl hydroxamate 136 from trans β -hydroxy carboxylate 135 (Scheme 24). Intramolecular cyclization of 136 under Mitsunobu conditions (Bellettini, J.R.; Miller, M.J. Tetrahedron Letters 1997, 38, 167-168) then affords benzyl protected hydroxy β -lactam 137. Removal of the benzyl group by hydrogenolysis and reduction of the intermediate N-hydroxy β -lactam provides 131, which can be converted to final products as shown in the previous scheme.

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Scheme 24

A synthesis of cyclic lactam β-amino acids begins conveniently with ketone 138 (Scheme 25). Oxime 139 is formed with hydroxylamine hydrochloride, sodium bicarbonate in refluxing methanol and is then treated with p-toluenesulfonyl chloride to give Beckmann rearrangement precursor 140. The rearrangement can be driven by a variety of conditions with silica gel/chloroform providing a straightforward mild procedure to form lactam 141. Conversion of 141 to hydroxamate 142 uses conditions outline in previous schemes.

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Scheme 25

Compounds of formula 147 can be prepared using the protocol described in Scheme 26. Alkylation of methyl 4-aminobenzoate or methyl 4-methylaminobenzoate 143 with 4-chloromethyl-2-methylquinoline using K_2CO_3 in DMF at 100 °C preduced the secondary or tertiary amine 144. Following saponification, the resulting carboxylic acid 145 was coupled with a cyclic β -aminoacid derivative using a coupling agent such as BOP to give the amide 146. Conversion of the ester in 146 to a hydroxamic acid using hydroxylamine afforded the final product 147.

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Scheme 26

Compounds of formula 154 can be prepared according to Scheme 27. An aldehyde 148 was treated with hydroxylamine to provide an oxime 149. Cycloaddition of 149 with an olefin 150 using bleach produced the isoxazoline derivative 151. Hydrolysis of the ester followed by coupling with a cyclic β -aminoacid derivative afforded the amide 153. Treatment of 153 with a hydroxylamine solution produced the hydroxamic acid 154.

Scheme 27

R¹=aryl, heteroaryl, alkyl, carbocycle, heterocycle

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Compounds of formula 161 can be prepared using the sequence as illustrated in Scheme 28. An aldehyde 155 was treated with hydroxylamine to give an oxime 156. Cycloaddition of 146 with an olefin 157 using bleach produced the isoxazoline derivative 158. Following saponification, the resulting carboxylic acid 159 was condensed with a cyclic β -aminoacid to give the amide 160. Treatment of 160 with a hydroxylamine solution afforded the hydroxamic acid 161.

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Scheme 28

R¹=aryl, heteroaryl, alkyl, carbocycle, heterocycle

One diastereomer of a compound of Formula I may display superior activity compared with the others. Thus, the following stereochemistries are considered to be a part of the present invention.

When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al, Antimicrobial Agents and Chemotheraphy, 1995, 2602-2605. A chiral compound of

Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., Andrew S. Thompson, et al, *Tetr. Lett.* **1995**, *36*, 8937-8940.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

10 Abbreviations used in the Examples are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, "¹H" for proton, "h" for hour or hours, "M" for molar, "min" for minute or minutes, "MHz" for megahertz, "MS" for mass spectroscopy, "NMR" for nuclear magnetic resonance spectroscopy, "rt" for room temperature, "tlc" for thin layer chromatography, "v/v" for volume to volume ratio. "α", "β", "R" and "S" are stereochemical designations familiar to those skilled in the art.

Example 1

N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-2'(trifluoromethyl)[1,1'-biphenyl]-4-carboxamide

(1a) Tetrakis(triphenylphosphine)palladium(0) (168 g, 0.1 eq) was added to a mixture of methyl-4-iodobenzoate (0.384 g, 1.44 mmol), 2-trifluoromethylphenylboronic acid (0.3 g, 1.1 eq), sodium carbonate (2 M, 2 eq), ethanol (1.5 mL) and benzene (1.5 mL) at rt. The mixture was heated to 70 °C for 24 h and cooled to rt. The mixture was diluted with ether (20 mL) and washed with water and brine (10 mL each), dried (MgSO₄) and concentrated. Silica gel column chromatography

(ethyl acetate-hexane, 5:95) yielded the desired product (364 mg, 90%). MS found: (M-H) = 279.

- (1b) The ester (364 mg, 1.3 mmol) from reaction (1a),
 5 lithium hydroxide (1 M, 10 eq) and methanol (13 mL) were stirred at 40 °C for 4.5 h. The pH of the mixture was adjusted to pH=3 with 1 N HCl and then extracted with ethyl acetate (2 x 30 mL), washed with brine (25 mL) dried (MgSO₄) and concentrated. Silica gel column chromatography (ethyl acetate-hexane, 1:1) yielded the desired product (247 mg, 71%). MS found: (M-H) =265.
- (1c) BOP reagent (239 mg, 1.2 eq) was added to a mixture of
 (1s,2R)-2-carbomethoxycyclopentyl amine hydrochloride (81

 15 mg, 0.45 mmol), the carboxylic acid (120 mg, 1 eq) from
 reaction (1b), N,N-diisopropylethylamine (0.12 mL, 2.5 eq)
 and N,N-dimethylformamide (2.5 mL) at rt. After 2.5 h at rt
 saturated aqueous ammonium chloride (25 mL) was added and
 the mixture extracted with ethyl acetate (2 x 20 mL). The

 20 mixture was washed with water (10 mL), brine (10 mL), dried
 (MgSO₄) and concentrated. Silica gel column chromatography
 (ethyl acetate-hexane, 1:3) yielded the desired product (147
 mg, 83%). MS found: (M+H) +=392.
- 25 (1d) Preparation of hydroxylamine/potassium hydroxide solution: A solution of potassium hydroxide (2.81 g, 1.5 eq) in methanol (7 mL) was added to a hot solution of hydroxylamine hydrochloride (2.34 g, 33.7 mmol) in methanol (12 mL). After the mixture was cooled to room temperature, the precipitate was removed by filtration. The filtrate was used fresh and assumed hydroxylamine concentration of 1.76 M.

The above freshly prepared 1.76 M hydroxylamine solution (0.5 mL, 4 eq) was added to the methyl ester (80 mg, 0.20 mmol) from reaction (1c) in methanol (1 mL) and

stirred at room temperature for 5 h. The mixture was adjusted to pH 7 with 1 N hydrochloric and diluted with ethyl acetate (10 mL). The organic layer was washed with brine (5 mL), dried (MgSO₄) and concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile 85-15 to 10-90) provided the hydroxamic acid (50 mg, 63%). MS found: (M+H) +=393.

Example 2

- 10 N-{(1R, 2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-4-[2-(trifluoromethyl)phenoxy]benzamide
- (2a) 4-hydroxybenzoic acid (240 mg, 1.6 mmol), 2trifluoromethylphenylboronic acid (300 mg, 1 eq), pyridine

 (0.68 mL, 5 eq), 4A molecular sieves (100 mg), copper (II)
 acetate (0.32 g, 1 eq) and dichloromethane (15 mL) were
 stirred under air atmosphere for 4 days. The mixture was
 filtered through Celite and the bed washed with ethyl
 acetate-hexane (1:9, 50 mL) and concentrated. Silica gel

 column chromatography (ethyl acetate-hexane, 1:10) yielded
 the desired product (49 mg, 10%). MS found: (M+H) += 296.
- (2b) Using procedures analogous to those described for reactions (1b)-(1d), the methyl ester (49 mg, 0.162 mmol) 25 from reaction (2a) was converted to the desired hydroxamic acid (2.6 mg, 4% for 3 steps). MS found: (M+H)+=409.

Example 3

- N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-4-(3methyl-2-pyridinyl)benzamide
 - (3a) Using procedures analogous to those described for reactions (1a)-(1d), 4-carbomethoxyphenylboronic acid (0.72 g, 2 eq) and 2-bromo-3-methylpyridine (0.34 g, 2.0 mmol)

were converted to the desired hydroxamic acid (40 mg, 10% for 4 steps). MS found: $(M+H)^+=340$.

Example 4

5 N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}[1,1'-biphenyl]-4-carboxamide

(4a) Using procedures analogous to those described for reactions (1c)-(1d), the amine hydrochloride (106 mg, 0.59 10 mmol) and 4-biphenylcarboxylic acid (117 mg, 1 eq) were converted to the desired hydroxamic acid (46.6 mg, 36% for 2 steps). MS found: (M+H)*=325.

Example 5

15 $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-4-$ phenoxybenzamide

(5a) Using procedures analogous to those described for reactions (1c)-(1d), the amine hydrochloride (111 mg) and 4-phenoxybenzoic acid (132 mg, 1 eq) were converted to the desired hydroxamic acid (24.2 mg, 36% for 2 steps). MS found: (M+H)+=341.

Example 6

25 4-(benzyloxy)-N-{(1R,2S)-2[(hydroxyamino)carbonyl]cyclopentyl}benzamide

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(6a) Using procedures analogous to those described for reactions (1c)-(1d), the amine hydrochloride (101 mg, 0.56 mmol), 4-benzyloxybenzoic acid (129 mg, 1 eq) were converted to the desired hydroxamic acid (19.1 mg, 26% for 2 steps). MS found: (M+H) +=355.

Example 7

 $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-2'$ methoxy[1,1'-biphenyl]-4-carboxamide

5 (7a) Using procedures analogous to those described for reactions (1a)-(1d), 2-methoxyphenylboronic acid (0.163 g, 1.1 eq), methyl 4-iodobenzoate (265 mg, 1.0 mmol) were converted to the desired hydroxamic acid (30 mg, 9% for 4 steps). MS found: (M+H) = 355.

10

Example 8

 $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-2'$ methyl[1,1'-biphenyl]-4-carboxamide

15 (8a) Using procedures analogous to those described for reactions (1a)-(1d), methyl 4-iodobenzoate (0.100 g, 0.4 mmol) and 2-methylphenylboronic acid (0.066 g, 1.2 eq) were reacted to give the desired hydroxamic acid (9.5 mg, 7% for 4 steps). MS found: (M+H)+=339.

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Example 9

 $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-4-(2-methoxyphenoxy)benzamide$

25 (9a) Using procedures analogous to those described for reactions (2a),(1b)-(1d),4-hydroxybenzoic acid (152 mg, 1.0 mmol) and 2-methoxyphenylboronic acid (304 mg, 2 eq), were reacted to give the desired hydroxamic acid (5.1 mg, 14% for 4 steps). MS found: (M+H)+=371.

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Example 10

 $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-4-(2-methylphenoxy)benzamide$

(10a) Using procedures analogous to those described for reactions (2a), (1b)-(1d), 4-hydroxybenzoic acid (152 mg, 1.0 mmol) and 2-methylphenylboronic acid (272 mg, 2 eq) were reacted to give the desired hydroxamic acid (23 mg, 7% for 4 steps). MS found: (M+H)⁺=355.

Example 11

 $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}^4-(3-methylphenoxy)benzamide$

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(11a) Using procedures analogous to those described for reactions (1a)-(1d), methyl 4-iodobenzoate (0.663 g, 0.2.5 mmol) and 3-methylphenylboronic acid (0.408 g, 1.2 eq) were reacted to give the desired hydroxamic acid (91.9 mg, 46% for 4 steps). MS found: $(M+H)^+=339$.

Example 12

4-(5,8-dihydro-4-quinolinyl)-N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}benzamide

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(12a) Using procedures analogous to those described for reactions (1a)-(1d), 4-carbomethoxyphenylboronic acid (298 mg, 2 eq) and 4-bromoquinoline were reacted to give the desired hydroxamic acid (25 mg, 9% for 4 steps). MS found: (M+H) +376.

Example 13

 $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-3',5'$ dimethyl[1,1'-biphenyl]-4-carboxamide

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(13a) Using procedures analogous to those described for reactions (1a)-(1d), 4-carbomethoxyphenylboronic acid (0.72 g, 2 eq) and 4-bromo-meta-xylene (0.37 g, 2.0 mmol) were reacted to give the desired hydroxamic acid (22 mg, 14% for 4 steps). MS found: $(M+H)^+=353$.

Example 14

 $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-6-(2-methylphenyl)nicotinamide$

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(14a) Using procedures analogous to those described for reactions (1a)-(1d), methyl 6-(3-methylphenyl)nicotinate (0.3 g, 1.4 mmol) and 2-methylphenylboronic acid (0.21 g, 1.1 eq) were reacted to give the desired product (18 mg, 17% for 4 steps). MS found: (M+H)⁺=340.

Example 15

 $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-6-(2-methoxyphenyl)nicotinamide$

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(15a) Using procedures analogous to those described for reactions (1a)-(1d), methyl 6-(3-methylphenyl)nicotinate (378 mg, 1.75 mmol) and 2-methoxyphenylboronic acid (292 mg, 1.1 eq) were reacted to give the desired product (10 mg, 6% for 4 steps). MS found: (M+H)+356.

Example 16

(3S, 4S) - N-hydroxy-1-isopropyl-4- $(\{4-[(2-methyl-4-quinolinyl)methoxy]benzoyl\}amino)-3-pyrrolidinecarboxamide$

25

- (16a) A solution of benzyl methyl maleate (15.0 g, 68.2 mmol) in benzene (1 L) at reflux was treated with a mixture of glycine (8.3 g, 2 eq) and para-formaldehyde (8.3 g, 4 eq) portionwise over 1 h. The mixture was heated at reflux for 2 h further. The mixture was filtered through a plug of silica and concentrated providing the desired amine (19.3 g, 100%). MS found: (M+H) +=264.
- (16b) The amine from reaction (16a) (7.3 g, 27.5 mmol) in N,N-dimethylformamide was treated with di-t-butyl

dicarbonate (9.0 g, 1.5 eq), triethylamine (5.8 mL, 1.5 eq), and hydroxylamine hydrochloride (0.2 g, 0.1 eq) and stirred for 17 h. The mixture was partitioned between water and ether (100 mL each) and the aqueous layer further extracted with ether (100 mL). The combined ether layers were washed with water and brine (100 mL each) dried (MgSO4) and concentrated. Silica gel column chromatography (ethyl acetate-hexane, 3:2) yielded the desired ester (6.39 g, 64%). MS found: (M-Bu)=308.

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(16c) The ester from reaction (16b) (8.3 g, 22.9 mmol) in methanol (100 mL) was treated with 10% palladium hydroxide on carbon (2.28 g, 0.1 eq) and stirred under a balloon of hydrogen for 3.5 h. The mixture was purged with nitrogen, filtered through a plug of Celite®, washed with excess

filtered through a plug of Celite®, washed with excess methanol, and the filtrate concentrated providing the desired acid (6.0 g, 96%). MS found: (M+Na)+296.

(16d) The acid from reaction (16c) (2.73 g, 0.01 mmol) in benzene (100 mL) was treated with triethylamine (2.1 mL, 1.5 eq) and diphenylphosphorylazide (2.58 mL, 1.2 eq) and stirred at room temperature for 1 h. Benzyl alcohol (1.03 mL, 1.0 eq) was added and the mixture heated to reflux for 1.5 h. The mixture was cooled and partitioned between ethyl acetate and saturated aqueous NaHCO₃ (100 mL each). The organic layer was washed further with NaHCO₃ and brine (100 mL each), dried (MgSO₄), and concentrated. Silica gel column chromatography (ethyl acetate-hexane, 3:2) yielded the desired carbamate (2.86 g, 76%). MS found: (M+H)+=379.

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(16e) The carbamate from reaction (16d) (2.86 g, 7.6 mmol) in methanol (38 mL) was treated with 10% palladium hydroxide on carbon (0.53 g, 0.1 eq) and stirred under a balloon of hydrogen for 1.5 h. The mixture was purged with nitrogen,

35 filtered through a plug of Celite®, washing with excess

methanol, and the filtrate concentrated providing the desired amine (1.85 g, 100%). MS found: (M-Bu)=189.

(16f) The amine from reaction (16e) (11 g, 45 mmol) in DMF
5 (225 mL) was treated with 4-[(2-methyl-4quinolinyl)methoxy]benzoic acid (19.8 g, 1.5 eq), BOP
reagent (32.1 g, 1.6 eq) and N,N-diisopropylethylamine (20
mL, 2.5 eq) and stirred for 5 h. The mixture was
partitioned between saturated aqueous NH4Cl and ethyl acetate
10 (500 mL each). The aqueous layer was further extracted with
ethyl acetate (3 X 500 mL). The combined layers were dried
(MgSO4) and concentrated. Silica gel column chromatography
(ethyl acetate) yielded the desired racemic amide (13 g).
Chiral HPLC separation provided the (3S,4S)-enantiomer (5.5
15 g, 23%, >98%ee), MS found: (M+H)*=520, and the (3R,4R)enantiomer (4.5 g, 19%). MS found: (M+H)*=520.

- (16g) The (3S,4S)-enantiomer from reaction (16f) (2.11 g, 4.06 mmol) in dichloromethane/trifluoracetic acid (1:1, 16 mL) was stirred for 1 h and concentrated. The residue was dissolved in water and lyophilized to provide the desired amine as the bis(trifluoroacetate) salt (2.6 g, 100%). MS found: (M+H)+420.
- 25 (16h) The amine from reaction (16g) (699 mg, 1.08 mmol) in dichloromethane (10 mL) was treated with N,N-diisopropylethylamine (0.77 mL, 4 eq), acetone (0.16 mL, 2 eq) and stirred at rt for 10 min. Na(OAc)₃BH (0.46 g, 2 eq) was then added and the mixture stirred for 1 h. The mixture was partitioned between ethyl acetate and saturated aqueous NaHCO₃ and then further extracted with ethyl acetate (4x). The organic layers were dried (MgSO₄) and concentrated. Silica gel column chromatography (methanol/dichloromethane, 1:4) yielded the desired amine (0.411 g, 89%). MS Found: 35 (M+H) +=462.

(16i) Preparation of hydroxylamine/potassium hydroxide solution: A solution of potassium hydroxide (2.81 g, 1.5 eq) in methanol (7 mL) was added to a hot solution of hydroxylamine hydrochloride (2.34 g, 33.7 mmol) in methanol (12 mL). After the mixture was cooled to room temperature, the precipitate was removed by filtration. The filtrate was used fresh and assumed hydroxylamine concentration of 1.76 M.

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The above freshly prepared 1.76 M hydroxylamine solution (7.6 mL, 15 eq) was added to the methyl ester (400 mg, 0.88 mmol) from reaction (16h) in methanol (9 mL) and stirred at room temperature for 0.5 h. The mixture was adjusted to pH 7 with 1 N hydrochloric acid and diluted with brine (50 mL) and extracted with dichloromethane (5 X 60 mL). The organic layers were dried (MgSO₄) and concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile 85-15 to 60-40, 0.1% TFA) provided the hydroxamic acid (207 mg, 34%). MS found: (M+H) +=463.

Example 17

(3S, 4S) -1-(2,2-dimethylpropanoyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3pyrrolidinecarboxamide

(17a) The amine from reaction (16g) (270 mg, 0.42 mmol) in dichloromethane (4 mL) was treated with triethylamine (0.57 mL, 10 eq), trimethylacetyl chloride (0.1 mL, 2 eq) and stirred at rt for 1 h. The mixture was partitioned between ethyl acetate and saturated aqueous NaHCO₃ and then further extracted with ethyl acetate (4x). The organic layers were dried (MgSO₄) and concentrated. Silica gel column chromatography (methanol/dichloromethane, 1:4) yielded the desired amide (189 mg, 90%). MS Found: (M+H) +=504.

(17b) Using procedures analogous to reaction (16i) the methyl ester from reaction (17a) (0.3 g, 6.0 mmol) was converted to the desired hydroxamic acid (107 mg, 30%). MS Found: (M+H) +=505.

Example 18

(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-(methylsulfonyl)-3-pyrrolidinecarboxamide

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(18a) The amine from reaction (16g) (206 mg, 0.33 mmol) in dichloromethane (3.3 mL) was treated with triethylamine (0.5 mL, 10 eq), methanesulfonyl chloride (0.05 mL, 2 eq) and stirred at rt for 1 h. The mixture was partitioned between ethyl acetate and saturated aqueous NaHCO₃ and then further extracted with ethyl acetate (4x). The organic layers were dried (MgSO₄) and concentrated. Silica gel column chromatography (methanol/dichloromethane, 1:4) yielded the desired amide (128 mg, 57%). MS Found: (M) +=498.

(18b) Using procedures analogous to reaction (16i), the methyl ester from reaction (18a) (224 mg, 4.5 mmol) was converted to the desired hydroxamic acid (104 mg, 37%). MS Found: (M+H)+=499

Example 19

(3S,4S)-N-hydroxy-1-methyl-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide

(19a) Using procedures analogous to those described for example (16h-i), the amine from reaction (16g) (0.324 g, 0.5 mmol) and formaldehyde (37%, 0.06 mL, 1.5 eq) were converted to the desired hydroxamic acid (155 mg, 25% 2 steps). MS Found: (M+H) *=435.

Example 20

(20a) 1,3-Pyrrolidinedicarboxylic acid, 4-oxo-1-(1,1-dimethylethyl) 3-methyl ester (2.45 g, 10.1 mmol) in benzene (50 mL) was treated with (R)-alpha-methylbenzyl amine (1.7 mL, 1.3 eq) and Yttrbium triflate (0.12 g, 0.02 eq) and heated to reflux for 3 h. Concentration, followed by silica gel column chromatography (ethyl acetate/hexane, 1:4) yielded the desired amine (2.49 g, 67%). MS Found: (M+H)⁺=347.

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(20b) The product from reaction (20a) (1.0 g, 2.9 mmol) in acetonitrile/acetic acid (1:1, 5.8 mL) was treated with NaBH₃CN and stirred for 0.5 h. The mixture was quenched with NaHCO₃ (aq) until pH 7 and extracted with ethyl acetate (3 X 100 mL). The combined layers were dried (MgSO₄) and concentrated. Silica gel column chromatography (ethyl acetate/hexane, 3:1) yielded the (3S,4S) amine (59.4 mg, 6%), MS Found: (M)*=349, the (3S,4R) amine (415 mg, 41% mmol) MS Found: (M)*=349 and the (3R,4S) amine (246 mg, 24%) MS Found: (M)*=349.

(20c) The (3S,4S) amine from reaction (20b) (59.4 mg, 0.17 mmol) in methanol/water/acetic acid (10:1:0.25, 1 mL) was treated with 10% palladium hydroxide on carbon (12 mg, 0.1 eq) and stirred under a balloon of hydrogen for 1.5 h. The mixture was purged with nitrogen, filtered through a plug of Celite®, washing with excess methanol and the filtrate concentrated providing the crude amine (37.9 mg) that was used without purification. In an analogous reaction to (1f)

the crude amine was converted to the desired amide (64.5 mg, 72% two steps). MS Found: $(M+H)^+=520$.

(20d) Using procedures analogous to reaction (16i), the methyl ester from reaction (20c) (60 mg, 0.12 mmol) was converted to the desired hydroxamic acid (42.4 mg, 58%). MS Found: (M+H) +=521.

Example 21

10 (3S,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide

(21a) In an analogous procedure to (16g) the product from reaction (20d) (12 mg, 0.02 mmol) was converted to the desired amine (8.7 mg, 72%). MS Found: (M+H)+=421.

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Example 22

tert-butyl 4-[cis-3-[(hydroxyamino)carbonyl]-4-({4-[(2methyl-4-quinolinyl)methoxy]benzoyl}amino)pyrrolidinyl]-1piperidinecarboxylate

(22a) In an analogous procedure to (16g) the racemic product from reaction (16h-16i) (0.25 g, 0.4 mmol) and Boc-4-piperidone (115 mg, 1.5 eq) was converted to the desired hydroxamic acid (49.4 mg, 18% 2 steps). MS Found: (M+H)+=604.

Example 23

cis-N-hydroxy-4-({4-[(2-methyl-4-30 quinolinyl)methoxy]benzoyl}amino)-1-(4-piperidinyl)-3pyrrolidinecarboxamide

(23a) In an analogous procedure to (16g) the product from reaction (22a) (25.2 mg, 0.03 mmol) was converted to the desired amine (21.4 mg, 82%). MS Found: (M+H) +=504.

Example 24

cis-1-[3-[(1,1-dimethylethoxy)carbonyl]pyrollidinyl]-N-hydroxy-3-[[[4-[(2-methyl-4-

quinolinyl)methoxy]phenyl]carbonyl]amino]-4pyrollidinecarboxamide bis(trifluoroacetate)

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(24a) In an analogous procedure to (1g) the racemic product
from reaction (16h-16i) (.25 g, 0.4 mmol) and Boc-310 pyrollidinone (107 mg, 1.5 eq) was converted to the desired
hydroxamic acid (73.1 mg, 26% 2 steps). MS Found:
(M+H)*=590.

Example 25

cis-N-hydroxy-1-[3-pyrollidinyl]-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-pyrollidinecarboxamide tris(trifluoroacetate)

(25a) In an analogous procedure to (16g), the product from reaction (24a) (31 mg, 0.04 mmol) was converted to the title compound (27.0 mg, 86%). MS Found: (M+H) +=490.

Example 26

tert-butyl (3R,4R)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-25 methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate

(26a) In an analogous procedure to (16h), the (3R,4R) enantiomer from reaction (16f) (0.2 g, 0.4 mmol) was
30 converted to the desired hydroxamic acid (18.3 mg, 7%). MS
Found: (M+H) += 521.

Example 27

tert-butyl (3S,4R)-3-[(hydroxyamino)carbonyl]-4-({4-[(2methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate

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(27a) In an analogous procedure to (20c-d), the (3S,4R)-amine from reaction (20b) (0.4 g, 1.2 mmol) was converted to the hydroxamic acid (53.6 mg, 20%, 2 steps). MS Found: $(M+H)^+=521$.

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Example 28

(3S,4R)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide

(28a) In an analogous procedure to (16g), the product from reaction (27a) (11 mg, 0.02 mmol) was converted to the desired amine (5 mg, 45%). MS Found: (M+H)+=421.

Example 29

tert-butyl (3R,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-20 methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate

(29a) In an analogous procedure to (20c-d), the (3R,4S)-amine from reaction (20b) (0.2 g, 0.6 mmol) was converted to the hydroxamic acid (132 mg, 59%, 2 steps). MS Found: (M+H)+=521.

Example 30

 $(3R,4S)-N-\text{hydroxy-4-}(\{4-[(2-\text{methyl-4-}\\quinolinyl)\text{methoxy}]\text{benzoyl}\}\text{amino})-3-pyrrolidinecarboxamide}$

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(30a) In an analogous procedure to (16g), the product from reaction (29a) (10 mg, 0.02 mmol) was converted to the desired amine (9.8 mg, 98%). MS Found: (M+H)⁺=421.

Example 31

N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-4-(4-pyridinyl)benzamide trifluoroacetate

(31a) Tetrakis(triphenylphosphine)palladium(0) (0.64 g, 0.1 eq) was added to a mixture of 4-methoxycarbonylphenyl-boronic acid (2.0 g, 11.1 mmol), 4-bromopyridine hydrochloride (1.03 g, 1 eq), sodium carbonate (2 M, 2 eq), methanol (10 mL) and benzene (10 mL) at rt. The mixture was heated to 70 °C for 2 h and cooled to rt. The mixture was diluted with ethyl acetate and saturated aqueous sodium bicarbonate (100 mL ea). The organic layers were washed with water and brine (100 mL each), dried (MgSO4), and concentrated. Silica gel column chromatography (ethyl acetate-hexane, 1:1) yielded the desired product (1.0 g, 85%). MS found: (M+H)+=214.

(31b) The ester (1.0 mg, 4.7 mmol) from reaction (31a), lithium hydroxide (1 M, 10 eq) and methanol (50 mL) were stirred at 40 °C for 2 h. The pH of the mixture was adjusted to pH=7 with 1 N HCl and then extracted with ethyl acetate (2 x 100 mL), dried (MgSO4), and concentrated, yielding the desired acid (400 mg, 43%). MS found: (M+H) +=200.

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(31c) BOP reagent (266 mg, 1.2 eq) was added to a mixture of (1R,2S)-2-carbomethoxycyclopentyl amine hydrochloride (90 mg, 0.50 mmol), the carboxylic acid (100 mg, 1 eq) from reaction (31b), N,N-diisopropylethylamine (0.22 mL, 2.5 eq) and N,N-dimethylformamide (1 mL) at rt. After 2.5 h at rt, saturated aqueous ammonium chloride (25 mL) was added and the mixture extracted with ethyl acetate (2 x 20 mL). The mixture was washed with water (10 mL), brine (10 mL), dried (MgSO4), and concentrated. Silica gel column chromatography

(ethyl_acetate) yielded the desired product (113 mg, 69%). MS found: $(M+H)^+=325$.

(31d) Freshly prepared 1.76 M hydroxylamine solution (8 mL, 20 eq) was added to the methyl ester (233 mg, 0.7 mmol) from reaction (31c) in methanol (1 mL) and stirred at room temperature for 0.5 h. The mixture was adjusted to pH 7 with 1 N hydrochloric acid and diluted with ethyl acetate (10 mL). The organic layer was washed with brine (5 mL), dried (MgSO4), and concentrated. Reverse phase HPLC purification (gradient elution, water/acetonitrile 85-15 to 10-90) provided the desired hydroxamic acid (83 mg, 35%). MS found: (M+H) *=326.

15 Example 32

- (3S, 4S) -1-(1, 1-dimethyl-2-propynyl) -N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide bis(trifluoroacetate)
- (32a) The amine from reaction (16g) (224 mg, 0.34 mmol) in dichloromethane (3 mL) was treated with triethylamine (0.24 mL, 5 eq), 3,3-dimethylpropargyl chloride (0.05 mL, 1.2 eq), water (1.5 mL), catalytic copper(I) chloride and catalytic copper turnings and stirred at rt for 1 h. The mixture was diluted with dichloromethane and washed with water (50 mL each), dried (MgSO4) and concentrated. Silica gel column chromatography (methanol/dichloromethane, 1:4) yielded the desired amine (150 mg, 89%). MS Found: (M+H) +=486.
- 30 (32b) In an analogous procedure to (16i) the ester from reaction (32a) (150 mg, 0.3 mmol) was converted to the desired hydroxamic acid (8.4 mg, 6%). MS Found: (M+H)+=487.

Example 33

(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-(2-propynyl)-3-pyrrolidinecarboxamide bis(trifluoroacetate)

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(33a) The amine from reaction (16g) (204 mg, 0.32 mmol) in dichloromethane (3 mL) was treated with triethylamine (0.18 mL, 4 eq), propargyl bromide (80% wt. in toluene, 0.04 mL, 1.1 eq) and stirred for 4 h. The mixture was partitioned between ethyl acetate and water (25 mL, ea) and the organic layer dried (MgSO₄), filtered and concentrated. Silica gel column chromatography (methanol/dichloromethane, 1:4) yielded the desired amine (38 mg, 26%). MS Found: (M+H)+458.

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(33b) In an analogous procedure to (16i), the ester from reaction (33a) (38 mg, 0.08 mmol) was converted to the desired hydroxamic acid (5 mg, 13%). MS Found: (M+H)+=459.

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Example 34

(3S,4S)-1-allyl-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide bis(trifluoroacetate)

25 (34a) Using analogous procedures to (33a-b), the amine from reaction (16g) (250 mg, 0.39 mmol) and allyl bromide (2 eq) was converted to the desired amine and then to the desired hydroxamate (92 mg, 47% 2 steps). MS Found: (M+H)+=461.

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Example 35

(3S, 4S) -N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-propyl-3-pyrrolidinecarboxamide bis(trifluoroacetate)

(35a) Using analogous procedures to (16h-i), the amine from reaction (16g) (250 mg, 0.39 mmol) and propanal (2 eq) was converted to the desired amine and then to the desired hydroxamic acid (38mg, 22% 2 steps). MS Found: (M+H)+=463.

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Example 36

(3S, 4S) -N-hydroxy-1-(2-methyl-2-propenyl)-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide bis(trifluoroacetate)

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(36a) Using analogous procedures to (33a), the amine from reaction (16g) (224 mg, 0.35 mmol) and 1-bromo-2-methyl propene (1.1 eq) was converted to the desired ester (110 mg, 67%). MS Found: (M+H)+=474.

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 $(M+H)^{+}=475$.

(36b) Preparation of hydroxylamine/sodium methoxide solution: hydroxylamine hydrochloride (2.4 g, 34.5 mmol) and MeOH (9 mL) were heated to 55 °C. Sodium methoxide (25% wt in MeOH, 11.85 mL, 1.5 eq) was added, the mixture stirred at 55 °C for 5 minutes and cooled to room temperature then 0 °C. Filtration afforded a clear solution assumed to be ca. 1.64 M. The solution is prepared and used fresh.

A solution of 1.64 M hydroxylamine solution (3 mL, 20 eq)
was added to the amine from reaction (36a) (110 mg, 0.45 mmol) in MeOH (3 mL) then stirred for 1h. The mixture was adjusted to pH 7 with 1 N hydrochloric acid (3 mL). Reverse phase HPLC purification (gradient elution, water/acetonitrile 85-15 to 60-40, 0.1% TFA) provided the hydroxamic acid (67 mg, 25%, 2 steps). MS Found:

Example 37

(3S, 4S)-1-(1,1-dimethyl-2-propenyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3pyrrolidinecarboxamide bis(trifluoroacetate)

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(37a) The amine from reaction (32a) (268 mg, 0.55 mmol) was treated with 5% Pd/BaSO4 (0.1 eq) in methanol (5.5 mL) and stirred under a balloon of hydrogen. The catalyst was removed by filtration and the mixture concentrated.

10 Silica gel column chromatography (methanol/dichloromethane, 1:4) yielded the desired olefin (150 mg, 56%) MS Found: (M+H)+488.

(37b) In an analogous procedure to (16i) the ester from reaction (37a) (106 mg, 0.2 mmol) was converted to the desired hydroxamic acid (50 mg, 32%). MS Found: (M+H)+=489.

Example 38

 $(3S, 4S) - N - hydroxy - 4 - (\{4 - [(2 - methyl - 4 - ((4 - [(3 - ((4 - [(3 - methyl - 4 - ((4 - [(3 - ((4 - ((4 - [(4 -$

(38a) The amine from reaction (37a) (61 mg, 0.13 mmol) was treated with 5% Rh/C (0.1 eq) in methanol (1.3 mL) and stirred under a balloon of hydrogen. The catalyst was removed by filtration and the mixture concentrated.

Silica gel column chromatography (methanol/dichloromethane, 1:4) yielded the desired amine (37 mg, 60%) MS Found: (M+H)+=

490.

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(38b) In an analogous procedure to (16i), the ester from reaction (38a) (37 mg, 0.08 mmol) was converted to the desired hydroxamic acid (14 mg, 25%). MS Found: (M+H)*=491.

Example 39

(3S, 4S) -N-hydroxy-1-isopentyl-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide bis(trifluoroacetate)

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(39a) Using analogous procedures to (16h and 36b), the amine from reaction (16g) (102 mg, 0.16 mmol) and isovaleral dehyde (3 eq) were converted to the desired amine and then to the desired hydroxamic acid (65 mg, 58% 2 steps). MS Found: $(M+H)^+=491$.

... Example 40

(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-neopentyl-3-pyrrolidinecarboxamide bis(trifluoroacetate)

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(40a) Using analogous procedures to (16h and 36b), the amine from reaction (16g) (60 mg, 0.1 mmol) and pivaldehyde (3 eq) was converted to the desired amine and then to the desired hydroxamic acid (44 mg, 64% 2 steps). MS Found: (M+H)⁺=491.

Example 41

(3S, 4S)-1-butyl-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide bis(trifluoroacetate)

(41a) Using analogous procedures to (16h and 36b), the amine from reaction (16g) (120mg, 0.19 mmol) and butyraldehyde (2 eq) were converted to the desired amine and then to the desired hydroxamic acid (20 mg, 15% 2 steps). MS Found: $(M+H)^+=477$.

Example 42

(3S,4S)-1-(3-butenyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide bis(trifluoroacetate)

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(42a) Using analogous procedures to (33a and 36b), the amine from reaction (16g) (216 mg, 0.33 mmol) and 4-bromo-1-butene (2 eq) were converted to the desired amine and then to the desired hydroxamic acid (68 mg, 30% 2 steps). MS Found: $(M+H)^+=475$.

Example 43

(3S, 4S) -1-(2-butynyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide bis(trifluoroacetate)

(43a) Using analogous procedures to (33a and 36b), the amine from reaction (16g) (140 mg, 0.22 mmol) and 1-bromo-2-butyne (1.2 eq) were converted to the desired amine and then to the desired hydroxamic acid (50 mg, 32% 2 steps). MS Found: $(M+H)^+=473$.

Example 44

(3S, 4S) -1-(2-furylmethyl) -N-hydroxy-4-({4-[(2-methyl-4quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide bis(trifluoroacetate)

(44a) Using analogous procedures to (16h and 36b), the amine from reaction (16g) (202 mg, 0.48 mmol) and furfural (1.5 eq) were converted to the desired amine and then to the desired hydroxamic acid (110 mg, 32% 2 steps). MS Found: $(M+H)^+=501$.

Example 45

(3S, 4S) -N-hydroxy-1-[(5-methyl-2-furyl)methyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3pyrrolidinecarboxamide bis(trifluoroacetate)

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(45a) Using analogous procedures to (16h and 36b), the amine from reaction (16 g) (223 mg, 0.53 mmol) and 5-methyl-furfural (1.5 eq) were converted to the desired amine and then to the desired hydroxamic acid (131 mg, 34% 2 steps).

10 MS Found: $(M+H)^+=515$.

Example 46

(3R,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)tetrahydro-3-furancarboxamide trifluoroacetate

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(46a) Sodium hydride (60% dispersion in mineral oil) (5.28 g, 1.1 eq) in ether (120 mL) was treated with methyl glycolate (10.8 g, 120 mmol) dropwise, slowly. The mixture was stirred for 30 min and cooled to 0°C. Methyl acrylate (12.39 g, 1.2 eq) was added dropwise to the 0°C solution. The mixture was stirred for 15 min, warmed to room temperature and stirred for 1 h. The reaction was cooled to 0°C and quenched by addition of 5% aqueous H₂SO₄ (200 mL). The layers were separated and the aqueous layer extracted with ether (2 X 250 mL). The combined ether layers were washed with brine (150 mL), dried with MgSO₄, filtered and concentrated. Flash chromatography (ethyl acetate/hexanes,

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(46b) The keto-ester (3.3 g, 23.0 mmol) from reaction (46a) in benzene (100 mL) was treated with (R)-alpha-methylbenzyl amine (3.0 mL, 1.02 eq) and yttrbium(III)triflate (0.29 g, 0.02 eq) and heated to reflux using Dean-Stark conditions for 3h, then treated with more (R)-alpha-methylbenzyl amine

75:25) provided the desired keto-ester (9.9 g, 57%).

(0.5 mL) and heated 1 h further. The solution was cooled to room temperature and washed with water (50 mL), dried with MgSO₄, filtered and concentrated. Flash chromatography (ethyl acetate/hexanes, 40:60) provided the desired enamine (2.7 g, 48%). MS found: (M+H)⁺=248.

- (46c) The enamine (3.43 g, 13.9 mmol) from reaction (46b) in acetic acid/dichloromethane/acētonitrile (1:1:1, 42 mL) was treated with NaBH(OAc), and stirred for 5 h. The

 10 reaction was cooled to 0°C and neutralized with saturated aqueous NaHCO, and extracted with dichloromethane (3 X 100 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (ethyl acetate/hexanes, 30:70) provided the desired amine (1.01 g, 29%) as a 3:1 mixture of

 15 diastereomers. MS found: (M+H)*=250.
- (46d) A mixture of the amine (838 mg, 3.38 mmol) from reaction (46c), 20% palladium hydroxide on carbon (240 mg, 0.1 eq) in methanol was shaken on a Parr apparatus under 50 psi of hydrogen for 2 h. The mixture was filtered and concentrated to provide the amine (495 mg, 100%). MS found: (M+H)*=146.
- (46e) A mixture of the amine (274 mg, 1.89 mmol) from

 reaction (46d) in DMF (10 mL) was treated with 4-[(2-methyl4-quinolinyl)methoxy]benzoic acid (691 mg, 1.25 eq), BOP

 reagent (1.23 g, 1.5 eq), N,N-diisopropylethylamine (1.0 mL,
 3.0 eq) and stirred for 5 h. The mixture was partitioned

 between saturated aqueous NH4Cl and ethyl acetate (25 mL

 acetate (3 X 50 mL). The combined layers were dried (MgSO4)

 and concentrated. Silica gel column chromatography

 (gradient elution: ethyl acetate to methanol/ethyl acetate

 1:10) yielded the desired amide (600 mg, 76%). MS found

 (M+H)*=421. Analytical chiral HPLC (Chiracel OD column, 1:1

hexane/ethanol, 0.75 mL/min, 254 nm) revealed a 77:23 mixture of enantiomers, which were separated on preparative scale (Chiracel OD column, 98:2 methanol/water) providing the faster running isomer (3S,4R)-enantiomer (120 mg, 15%, >98%ee) and the slower running (3R,4S)-enantiomer (440 g, 55%, >98%ee).

(46f) Using conditions similar to those described for reaction (36b), the slower running (3R,4S) isomer (130 mg, 0.3 mmol) was converted to the desired hydroxamic acid (108 mg, 65%). MS Found: (M+H) = 422.

Example 47

(3S, 4R) -N-hydroxy-4-({4-[(2-methyl-4quinolinyl)methoxy]benzoyl}amino)tetrahydro-3furancarboxamide trifluoroacetate

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(47a) Using conditions similar to those described for reaction (36b), the faster running (3S,4R) isomer (38 mg, 0.09 mmol) was converted to the desired hydroxamic acid (45 mg, 92%). MS Found: (M+H)⁺=422.

Example 48

 $(3S, 4S) - N - hydroxy - 4 - (\{4 - [(2 - methy 1 - 4 - a)]\})$

25 quinolinyl)methoxy]benzoyl}amino)-1-(1,3-thiazol-2-ylmethyl)-3-pyrrolidinecarboxamide bis(trifluoroacetate)

(48a) Using analogous procedures to (16h) and (36b), the amine from reaction (16g) (229 mg, 0.55 mmol) and 2-thiazolecarboxaldehyde (1.5 eq) were converted to the desired amine and then to the desired hydroxamic acid (186 mg, 46%, 2 steps). MS Found: $(M+H)^{+}=518$.

Example 49

(3S,4S)-1-acetyl-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide trifluoracetate

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(49a) A BIO-RAD Poly-Prep® chromatography column (0.8 x 4 cm) vessel was charged with a solution of the free base of the amine from reaction (16g) (0.1 g, 0.24 mmol) in dichloromethane (4 mL). The mixture was then treated with PS-DIEA resin (Argonaut Technologies) (215 mg, 3 eq) followed by acetyl chloride (0.026 mL, 1.5 eq). The vessel was sealed and rotated on a Labquake® rotisserie (Barnstead/Thermolyne) for 2 h. PS-Trisamine resin (Argonaut Technologies) (300 mg, 3 eq) was then added, the vessel sealed and rotated for 1 h. The reaction mixture was then filtered and the resins rinsed with dichloromethane (4 mL). The filtrate was concentrated in a test tube to give the desired amide as a white solid that was taken on without further purification. MS found: (M+H)*=462.

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(49b) The crude amide from reaction (49a), in a test tube, was treated with a 1.64M solution of NH2OH/NaOMe/MeOH, as prepared in example (36b) (2.9 mL, 20 eq), at 0°C and warmed to ambient temperature while agitating on a Vortex (1 h).
25 The mixture was quenched with 1N HCl (2.9 ml) and the ensuing precipitate filtered affording a white solid. The product was converted to its TFA salt by dissolution in 0.2 N TFA (5 mL), filtration through a 0.45 μ PTFE membrane, and freeze-drying yielding the desired hydroxamate as a white
30 amorphous solid (90.7 mg, 66% yield, 2 steps). MS Found: (M+H)*=463.

Example 50

(3S,4S)-N-hydroxy-1-isobutyryl-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide trifluoracetate

(50a) Using procedures analogous to (49a)-(49b), the free base of the amine from reaction (16g) (0.1g, 0.24 mmol) and isobutyryl chloride (0.038 mL, 1.5 eq) were converted to the desired amide and then to the desired hydroxamic acid (112 mg, 77% yield, 2 steps). MS Found $(M+H)^{+}=491$.

Example 51

(3S,4S)-N-hydroxy-1-(3-methylbutanoyl)-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide trifluoracetate

(51a) Using procedures analogous to (49a)-(49b), the free base of the amine from reaction (16g) (0.1g, 0.24 mmol) and 3-methylbutanoyl chloride (0.044 mL, 1.5 eq) were converted to the desired amide and then to the desired hydroxamic acid (116 mg, 78% yield, 2 steps). MS Found (M+H)*=505.

Example 52

20 (3S,4S)-1-(cyclopropylcarbonyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide trifluoracetate

(52a) Using procedures analogous to (49a)-(49b), the free base of the amine from reaction (16g) (0.1g, 0.24 mmol) and cyclopropanecarbonyl chloride (0.033 mL, 1.5 eq) were converted to the desired amide and then to the desired hydroxamic acid (40 mg, 28% yield, 2 steps). MS Found (M+H)+=489

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Example 53

(3S, 4S)-1-(cyclobutylcarbonyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide trifluoracetate

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(53a) Using procedures analogous to (49a)-(49b), the free base of the amine from reaction (16g) (0.1g, 0.24 mmol) and cyclobutanecarbonyl chloride (0.042 mL, 1.5 eq) were converted to the desired amide and then to the desired hydroxamic acid (83 mg, 56% yield, 2 steps). MS Found (M+H)+=503.

Example 54

(3S,4S)-N-hydroxy-1-(methoxyacetyl)-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide trifluoracetate

(54a) Using procedures analogous to (49a)-(49b), the free base of the amine from reaction (16g) (0.1g, 0.24 mmol) and methoxyacetyl chloride (0.033 mL, 1.5 eq) were converted to the desired amide and then to the desired hydroxamic acid (85 mg, 59% yield, 2 steps). MS Found (M+H) +=493.

Example 55

20 (3S,4S)-1-(2-furoyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide trifluoracetate

(55a) Using procedures analogous to (49a)-(49b), the free base of the amine from reaction (16g) (0.1g, 0.24 mmol) and 2-furoyl chloride (0.036 mL, 1.5 eq) were converted to the desired amide and then to the desired hydroxamic acid (75 mg, 50% yield, 2 steps). MS Found (M+H)*=515.

30 Example 56

(3S, 4S) -N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-(2-thienylcarbonyl)-3-pyrrolidinecarboxamide trifluoracetate

35 (56a) Using procedures analogous to (49a)-(49b), the free base of the amine from reaction (16g) (0.1g, 0.24 mmol) and

2-thienylcarbonyl chloride (0.039 mL, 1.5 eq) were converted to the desired amide and then to the desired hydroxamic acid (70 mg, 46% yield, 2 steps). MS Found (M+H)*=531.

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Example 57

(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4quinolinyl)methoxy]benzoyl}amino)-1-propionyl-3pyrrolidinecarboxamide trifluoracetate

10 (57a) Using procedures analogous to (49a)-(49b), the free base of the amine from reaction (16g) (0.1g, 0.24 mmol) and propionyl chloride (0.031, 1.5 eq) were converted to the desired amide and then to the desired hydroxamic acid (71 mg, 51% yield, 2 steps). MS Found (M+H) *=477.

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Example 58

(3R,4S)-4-{[4-(2-butynyloxy)benzoyl]amino}-N-hydroxy-tetrahydro-3-furancarboxamide

20 (58a) Using procedures analogous to (1c) and (16i) the amine from reaction (46d) (31 mg, 0.21 mmol, 52%ee) and (49 mg, 1.2 eq) were converted the amide and then hydroxamic acid (22 mg, 33%). MS Found (M+H)*=319.

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Example 59

N-{(1R,2S)-2-[(hydroxyamino)carbonyl]-4-oxocyclopentyl}-4-[(2-methyl-4-quinolinyl)methoxy]benzamide trifluoroacetate

(59a) 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide 30 hydrochloride (73.0 g, 1.5 eq) was added to a mixture of (1S,2R)-1-methyl cis-1,2,3,6-tetrahydrophthalate (46.8 g, 254.2 mmol), benzyl alcohol (30.2 g, 1.1 eq) and 4dimethylaminopyridine (3.0 g, 0.1 eq) in dichloromethane (470 mL) at 0°C and let warm to room temperature. After 3

35 h, the solution was cooled to 0°C and 1N HCl (300 mL) was

added. The mixture was extracted with dichloromethene (2 X 300 mL). The organic layer was washed successively with brine (200 mL), dried (MgSO₄) and concentrated. 70 g of crude product was obtained and purified by silica gel column chromatography (ethyl acetate-hexane (1:10). The desired compound was obtained as colorless oil (68.8 g, 99%). MS found: (M+H)⁺=275.

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- (59b) The olefin from reaction (59a) (68.8 g, 251 mmol) was 10 added dropwise to a solution of potassium permanganate (125 g, 3.2 eq) in water (400 mL) at 0°C. After 20 min stirring at 0°C, TLC showed the presence of starting olefin. Another portion of water (400 mL) and potassium permanganate (125 g) were added. After 20 min the reaction was complete (by 15 TLC). Sulfur dioxide was bubbled through the mixture at 0°C until the color of the solution turned pink from purple (2 The mixture was filtered and the filtrate was acidified by adding concentrated HCl to pH=1. The reaction was extracted with ethyl acetate (5 X 500 mL) and the combined 20 organic layers were dried over sodium sulfate. After filtration and concentration, the target diacid was obtained (74 g, 87% yield) and taken on without further purification. MS found: MS found: $(M+H)^{+}=339$.
- 25 (59c) Sodium acetate (11.4 g, 138 mmol) was added to a solution of the dicarboxylic acid from reaction (59b) (57 g, 169 mmol) in acetic anhydride (43 g, 421 mmol) at rt. The reaction was refluxed for 2h, and cooled to rt. Acetic anhydride was removed by rotary evaporation under reduced 30 pressure. Water (600 mL) was added and the residue was extracted with ethyl acetate (1 L X 2). The combined organic layers were dried over MgSO₄. After filtration and concentration, the crude ketone was obtained. Purification by silica gel column chromatography (Ethyl acetate 33% in hexane) furnished the target ketone (21 g, 45% yield). MS found: (M)*=276.

(59d) The ketone from reaction (59c)(7g, 25.3mmol), ethylene glycol (15.7 g, 253.3 mmol) and p-toluenesulfonic acid monohydrate (481 mg, 2.5 mmol) were refluxed in benzene (507 mL) using Dean-Stark conditions for 1h. After cooling, the reaction was quenched with saturated sodium bicarbonate solution (80mL) and extracted with ethyl acetate (2 X 100mL). The combined organic layers were washed with brine (80 mL), dried over magnesium sulfate, filtered and concentrated. The purification by silica gel column chromatography (Ethyl acetate 33% in hexane) furnished the target ketal (7.8 g, 97% yield). MS found: (M+H)*=321.

(59e) The ketal from reaction (59d) (7.1 g, 22.3 mmol) and palladium hydroxide on carbon (20 wt%, 780 mg, 0.1 e q) were stirred in ethyl acetate (11 mL) under hydrogen (balloon) at rt for 45 min. After filtration and concentration, the target carboxylic acid (5.1 g, 99% yield) was obtained. MS found: (M+H) =231.

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(59f) To a solution of the carboxylic acid from reaction (59e) (447 mg, 1.9 mmol) in acetone was added triethylamine (393 mg, 3.9 mmol) and ethyl chloroformate (316 mg, 2.9 mmol) at -25°C under nitrogen. After stirring at rt for 10 min, sodium azide (316 mg, 4.9 mmol) dissolved in water (0.5 mL) was added to the mixture at -10°C. The reaction was stirred at rt for 1h, and quenched with water (20 mL). It was extracted with CH,Cl, (2 X 50 mL), washed with brine (30 mL), dried over MgSO4, filtered, and concentrated. The crude azide was dissolved in benzene (2.6 mL) and refluxed for 1h. Benzyl alcohol (210 mg, 1.9 mmol) and p-toluenesulfonic acid (18 mg, 0.1 mmol) were added and the mixture was refluxed for 1h. After cooling to rt, the reaction was quenched with water and extracted with CH_Cl_ (2 X 50 mL). The combined organic layer was washed with brine (50 mL), dried over MgSO, filtered, and concentrated. The crude was purified by

silica gel column chromatography (33%EtOAc in hexane). The target amide (393 mg, 60% yield) was obtained. MS found: $(M+H)^{+}=236$.

- 5 (59g) The Cbz protected amine from reaction (59f) (3.8 g, 11.3 mmol), triethylamine (1.1 g, 11.3 mmol) and palladium hydrooxide on carbon (20 wt%, 400 mg, 0.56 mmol) were stirred in EtOAc (57mL) under hydrogen (50psi) at rt for 2h. After filtration and concentration, the target amine was obtained (2.2 g, 96% yield). MS found: (M+H) =202.
- (59h) To the solution of the amine from reaction (59g) (2.2
 g, 11.3 mmol), 4-[(2-methyl-4-quinolinyl)methoxy]benzoic
 acid (3.49 g, 11.9 mmol) and diisopropylethylamine (3.7 g,
 15 28.3 mmol) in DMF (57 mL) was added BOP reagent (6 g, 13.6
 mmol) at 0°C. After stirring at rt for 3h, the reaction was
 quenched with NH₄Cl (100 mL) at 0°C, extracted with EtOAc
 (300 mL X 2), washed with brine (100 mL), dried over Na₂SO₄,
 filtered and concentrated. The crude (14g) was purified by
 20 silica gel column chromatography (Gradient elution ethyl
 acetate/hexane, 1:1 to ethyl acetate) to give the target
 compound amide (5.4 g, 99% yield). MS found: (M+H)*=477.
- (59i) Using conditions analogous to (36b) and the ester from reaction (59h) (300 mg, 0.63 mmol) was converted to the desired hydroxamic acid (220 mg, 73% yield. (M+H) +478.
- (59j) The compound from reaction (59i) (24 mg, 0.0511 mmol) was dissolved in TFA (5 mL). After 10 min stirring at rt, TFA was evaporated. The crude was dissolved in DMSO and purified by HPLC. The TFA salt of target hydroxyamine compound was obtained (28 mg, 99% yield). MS found: (M+H)*=434.

Example 60

 $N-\{(1R, 2S, 4R)-4-hydroxy-2-$

[(hydroxyamino)carbonyl]cyclopentyl}-4-[(2-methyl-4-quinolinyl)methoxy]benzamide trifluoracetate

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- (60a) The compound from reaction (59h) (47 mg, 0.1 mmol) in THF (0.4 mL) was treated with HCl (3N solution, 0.4 mL) at rt for 3h. The reaction was quenched with saturated NaHCO3 to basic solution at 0°C. The mixture was extracted with ethyl acetate (20 mL X 2), washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated. Silica gel chromatography (dichloromethane/methanol, 20:1) provided the desired ketone (25 mg, 59 % yield). MS found: (M+H)⁺=231
- 15 (60b) To a solution of the ketone from reaction (60a) (520 mg, 1.2 mmol) in MeOH (120 mL) was added NaBH, at 0°C. The reaction was stirred at rt for 20 min. MeOH was evaporated. The reaction was diluted with ethyl acetate and quenched with saturated aqueous NH,Cl at 0°C. White solid was 20 filtered and the filtrate was extracted with EtOAc (200 mL X 2), dried over Na₂SO₄, filtered and concentrated. The crude alcohol was purified by silica gel column chromatography (5% MeOH in CH₂Cl₂) to give two diastereomers. Major diastereomer (380 mg, 73% yield) and minor one (95 mg, 18%) were obtained. MS found: (M+H) *=435.
 - (60c) Using conditions analogous to (36b) and the major diastereomer from reaction (60b) (50 mg, 0.12 mmol) was converted to the desired hydroxamic acid (29 mg, 46% yield. $(M+H)^+=436$.

Example 61

 $N-\{(1R, 2S, 4S)-4-hydroxy-2-$

[(hydroxyamino)carbonyl]cyclopentyl}-4-[(2-methyl-4-quinolinyl)methoxy]benzamide trifluoracetate

(61a) Using conditions analogous to (36b) the minor diastereomer from reaction (60b) (50 mg, 0.12 mmol) was converted to the desired hydroxamic acid (57 mg, 91% yield. (M+H) = 436.

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Example 62

(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-tetrahydro-2H-pyran-4-yl-3-pyrrolidinecarboxamide bis(trifluoroacetate)

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(62a) Using analogous procedures to (16h and 36b), the amine from reaction (16g) (205 mg, 0.49 mmol) and tetrahydro-4H-pyran-4-one (0.068 mL, 1.5 eq) were converted to the desired amine and then to the desired hydroxamic acid (100 mg, 28%, 2 steps). MS Found: $(M+H)^{+}=505$.

Example 63

methyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-pyrrolidinecarboxylate trifluoroacetate

(63a) A BIO-RAD Poly-Prep® chromatography column (0.8 X 4 cm) vessel was charged with a solution of the free base of the amine from reaction (16 g) (0.1 g, 0.24 mmol) in dichloromethane (6 mL). The mixture was then treated with PS-DIEA resin (Argonaut Technologies) (215 mg, 3 eq) followed by methylchloroformate (0.028 mL, 1.5 eq). The vessel was sealed and rotated on a Labquake® rotisserie (Barnstead/Thermolyne) for 6h. PS-Trisamine resin (Argonaut Technologies) (300 mg, 3 eq) was then added, the vessel sealed and rotated for 16h. The reaction mixture was then filtered and the resins rinsed with dichloromethane (4 mL). The filtrate was concentrated in a test tube to give the desired carbamate as a white solid that was taken on without further purification. MS found: (M+H)*=478.

(63b) The crude carbamate from reaction (49a), in a test tube, was treated with a 1.64M solution of NH2OH/NaOMe/MeOH, as prepared in example (36b) (2.9 mL, 20 eq), at 0°C and warmed to ambient temperature while agitating on a Vortex (1 h). The mixture was quenched with 1N HCl (2.9 ml) and the ensuing precipitate filtered affording a white solid. The product was converted to its TFA salt by dissolution in 0.2 N TFA (5-mb); filtration through a 0.45 μ PTFE membrane, and freeze-drying yielding the desired hydroxamate as a white amorphous solid (119 mg, 84% yield, 2 steps). MS Found: (M+H)*=479.

Example 64

ethyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-pyrrolidinecarboxylate trifluoracetate

(64a) Using procedures analogous to (63a)-(63b), the free base of the amine from reaction (16g) (0.1g, 0.24 mmol) and ethylchloroformate (0.034 mL, 1.5 eq) were converted to the desired carbamate and then to the desired hydroxamic acid (136 mg, 94% yield, 2 steps). MS Found (M+H)*=493.

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Example 65

propyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-pyrrolidinecarboxylate trifluoroacetate

(65a) Using procedures analogous to (63a)-(63b), the free base of the amine from reaction (16g) (0.1g, 0.24 mmol) and propylchloroformate (0.040 mL, 1.5 eq) were converted to the desired carbamate and then to the desired hydroxamic acid (134 mg, 90% yield, 2 steps). MS Found (M+H)*=507.

Example 66

allyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-pyrrolidinecarboxylate trifluoroacetate

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(66a) Using procedures analogous to (63a)-(63b), the free base of the amine from reaction (16g) (0.1g, 0.24 mmol) and allylchloroformate (0.038 mL, 1.5 eq) were converted to the desired carbamate and then to the desired hydroxamic acid (122 mg, 82% yield, 2 steps). MS Found $(M+H)^{+}=505$.

Example 67

isopropyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate trifluoroacetate

(67a) Using procedures analogous to (63a)-(63b), the free base of the maine from reaction (16g) (0.1g, 0.24 mmol) and isopropylchloroformate (1M in toluene, 0.36 mL, 1.5 eq) were converted to the desired carbamate and then to the desired hydroxamic acid (127 mg, 85% yield, 2 steps). MS Found (M+H) = 507.

Example 68

25 2-propynyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate trifluoroacetate

(68a) Using procedures analogous to (63a)-(63b), the free base of the amine from reaction (16 g) (0.1 g, 0.24 mmol) and 2-propynylchloroformate (0.035 mL, 1.5 eq) were converted to the desired carbamate and then to the desired hydroxamic acid (88 mg, 60% yield, 2 steps). MS Found (M+H)*=503.

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Example 69

2-butynyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate trifluoroacetate

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(69a) Using procedures analogous to (63a)-(63b), the free base of the amine from reaction (16g) (0.1g, 0.24 mmol) and 2-butynylchloroformate (0.041 mL, 1.5 eq) were converted to the desired carbamate and then to the desired hydroxamic acid (96 mg, 63% yield, 2 steps). MS Found $(M+H)^+=517$.

Example 70

3-butenyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate trifluoroacetate

(70a) Using procedures analogous to (63a)-(63b), the free base of the amine from reaction (16 g) (0.1 g, 0.24 mmol) and 3-butenylchloroformate (0.045 mL, 1.5 eq) were converted to the desired carbamate and then to the desired hydroxamic acid (109 mg, 72% yield, 2 steps). MS Found (M+H)⁺=519.

Example 71

benzyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-25 4-quinolinyl)methoxy]benzoyl}amino)-1-pyrrolidinecarboxylate trifluoroacetate

(71a) Using procedures analogous to (63a)-(63b), the free base of the amine from reaction (16g) (0.1g, 0.24 mmol) and benzylchloroformate (0.051, 1.5 eq) were converted to the desired carbamate and then to the desired hydroxamic acid (98 mg, 61% yield, 2 steps). MS Found (M+H) =554.

Example 72

 $N-\{(1R,2S)-4-(dimethylamino)-2-$

[(hydroxyamino)carbonyl]cyclopentyl}-4-[(2-methyl-4-quinolinyl)methoxy]benzamide bis(trifluoroacetate

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(72a) Using procedures analogous to examples (36a) and (36b) the ketone from example (60a) (50mg, 0.12mmol) and dimethyl amine were converted to the desired amine and then the desired hydroxamic acid (74 mg, 27% yield). MS found: (M+H)+=463

Example 73

(3S, 4S) -4-{[4-(2-butynyloxy)benzoyl]amino}-N-hydroxy-1-isopropyl-3-pyrrolidinecarboxamide

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(73a) The amide from reaction (16g) (510 mg, 1.10 mmol) in AcOH (2 mL) and dichloromethane (4 mL) was treated with zinc dust (217 mg, 3 eq)) and stirred for 24 h at ambient temperature. The remaining zinc was filtered off and the filtrate neutralized with saturated aqueous NaHCO3 (5 mL) and extracted with ethyl acetate (3 X 10 mL). The combined extracts were dried (MgSO₄) and concentrated. Silica gel chromatography (ethyl acetate) provided the desired phenol (259 mg, 77%). MS Found: (M+H) 307.

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(73b) 2-Butyn-1-ol (105 mg, 1.5 eq)) was treated with triphenylphosphine (393 mg, 1.5 eq.) and diethylazodicarboxylate (0.24 mL, 1.5 eq) in benzene (10 mL). The phenol from reaction (73a) (307 mg, 1.0 mmol) in benzene (5 mL) was added via cannula and the mixture stirred for 12 h. The mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dries (MgSO₄), filtered and concentrated. Silica gel chromatography (ethyl acetate) provided the desired ether (200 mg, 45%). MS Found: (M+H)*=459.

(73c) Using procedures analogous to (36b), the ester from reaction (73b) (200 mg, 0.44 mmol) was converted to the desired hydroxamic acid (57 mg, 28% yield). MS Found $(M+H)^{+}=360$.

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Example 74

N-{(1R,2S)-4,4-difluoro-2-

[(hydroxyamino)carbonyl]cyclopentyl}-4-[(2-methyl-4-quinolinyl)methoxy]benzamide trifluoroacetate

(74a) To a heterogeneous solution of the ketone from example (60a) (50 mg, 0.12 mmol) in toluene (0.5 mL) was added diethylaminosulfur trifluoride (47 mg, 0.29 mmol) at 0°C. The reaction was stirred at rt for 3 days. The mixture was poured into ice water, extracted with EtOAc (10 mL X 2), dried over Na₂SO₄, filtered and concentrated. Crude 60mg was

purified by silica gel column chromatography (EtOAc 90% in hexane). The target difluoride compound (18 mg, 34% yield)

20 was obtained. MS found: (M+H) =455.

(74b) Using conditions analogous to (36b) and the ester from example (74a) (18 mg, 0.0.04 mmol) was converted to the desired hydroxamic acid (11 mg, 49% yield. (M+H) =456.

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Example 75

(3S,4S)-N-hydroxy-1-isopropyl-4-{[4-(2-methylphenoxy)benzoyl]amino}-3-pyrrolidinecarboxamide trifluoroacetate

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(75a) Using procedures analogous to (2a) and (36b), The phenol from reaction (73a) (100 mg, 0.33 mmol) and 2-methylphenylboronic acid (135 mg, 0.4 mmol) were converted the desired ester and then hydroxamic acid (23 mg, 41% yield). MS Found: (M+H)*=398.

Example 100

cis-N-hydroxy-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-1cyclopentanecarboxamide -trifluoroacetate

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(100a) A mixture of methyl (+/-)-cis-2aminocyclopentanecarboxylate hydrochloride (150 mg, 0.83
mmol), 4-(2-methyl-4-quinolinylmethoxy)benzoic acid (250 mg,
1 eq), DIEA (0.43 mL, 3 eq) and BOP (0.31 g, 1.2 eq) in DMF
(4 mL) was stirred at rt for 2 h. Following addition of sat
NH₄Cl, the mixture was extracted with ethyl acetate. The
extracts were washed with sat NaHCO₃, brine, dried (MgSO₄)
and concentrated in vacuo. Silica gel chromatography (ethyl
acetate-hexane, 60:40 then 80:20) provided the desired amide
(330 mg, 95%). MS (M+H)⁺=419.

(100b) The freshly prepared 1.76 M solution of hydroxylamine (3.0 mL, 9 eq) was added to the ester from (100a) (240 mg, 0.57 mmol) at rt. After 30 min at this temperature, the mixture was acidified to pH 5 with 4 N HCl. The desired hydroxamic acid precipitated out and collected by filtration (146 mg, 61%). The free base was then converted to the trifluoroacetate salt in quantitative yield by reaction with TFA. MS found: (M+H)⁺=420.

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Example 101

trans-N-hydroxy-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-1cyclopentanecarboxamide trifluoroacetate

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(101a) The cis-isomer from (100a) (90 mg, 215 mmol) was dissolved in toluene (10 mL) and heated to reflux for 45 h. The mixture was filtered through a pad of silica gel and filter pad washed with EtOAc until free of product. The

filtrate was concentrated to give a 1:1 mixture of trans and cis isomers (77.2 mg, 86%). MS found: (M+H) +=419.

(101b) Following a procedure similar to that used for step (100b), the title compound was prepared. The two isomers were separated by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the trans hydroxamic acid product (25%). MS (M+H) +420.

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Example 102

(1S, 2R) -N-hydroxy-2-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-cyclopentanecarboxamide trifluoroacetate

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(102a-b) Following the procedures similar to that used for steps (100a-b), but using methyl (1S, 2R)-2-aminocyclopentanecarboxylate hydrochloride (Davies, S. G.; Ichihara, O.; Lenoir, I.; Walters, A. S. J. Chem. Soc.

20 Perkin Trans. 1994, 1411), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS

(M+H) +=420.

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Example 103

(1R,2S)-N-hydroxy-2-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-cyclopentanecarboxamide trifluoroacetate

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(103a-b) Following the procedures similar to that used for steps (100a-b), but using methyl (1R, 2S)-2-aminocyclopentanecarboxylate hydrochloride (Davies, S. G.; Ichihara, O.; Lenoir, I.; Walters, A. S. J. Chem. Soc.

Perkin Trans. 1994, 1411), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS

(M+H) +=420.

Example 104

cis-N-hydroxy-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-1cyclohexanecarboxamide trifluoroacetate

(104a-b) Following the procedures similar to that used for steps (100a-b), but using (+/-)-cis-2-aminocyclohexanecarboxylate hydrochloride, the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=434.

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Example 105

trans-N-hydroxy-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-1cyclohexanecarboxamide trifluoroacetate

25 (105a-b) Following the procedures similar to that used for steps (101a-b), but using the cyclohexane analogue, the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic 30 acid product. MS (M+H) +=434.

Example 108

trans-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-3-[[[4[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4pyrrolidinecarboxamide trifluoroacetate

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(108a) A solution of benzyl methyl fumarate (26.4 g, 113 mmol) in toluene (200 mL) was heated to reflux. A suspension of glycine (11.0 g, 1.3 eq) and para-formaldehyde (4.40 g, 1.3 eq) in toluene (50 mL) was added over 1 h. The mixture was maintained at reflux for 2 h after completion of addition. Additional amount of para-formaldehyde (1 eq) and glycine (1 eq) were added. After additional 30 min at reflux, the mixture was cooled and filtered. The filtrate was diluted with ethyl acetate (300 mL) and washed with sat Na2CO3 (2 x 10 mL), brine (10 mL), dried (MgSO4) and concentrated. The crude material was used in the next step without purification. MS (M+H) +=278.

(108b) DIEA (34.8 mL, 1.8 eq) and (BOC)₂O (36.3 mL, 1.5 eq)
were added to a solution of the crude amine from (108a) in CH₂Cl₂ (600 mL) at 0 °C. After 2 days at rt, additional amount of DIEA (1 eq) and (BOC)₂O (1 eq) were added. After a total of 3 days, the mixture was washed with sat NaHCO₃ (2 x 20 mL), brine (20 mL), dried (MgSO4) and concentrated in vacuo. Silica gel chromatography (ethyl acetate-hexane, 10:90 then 20:80) provided the desired product (7.60 g, 20% over 2 steps). MS (M+H) +378.

(108c) A mixture of the benzyl ester from (108b) (7.40 g, 19.6 mmol) and Pd(OH)₂ on carbon (1.90 g) in methanol (150 mL) was purged with hydrogen and stirred under balloon pressure hydrogen for 3 h. The catalyst was removed by filtration and the filtrate was concentrated to give the desired carboxylic acid (5.64 g, 100%). MS (2M-H) =573.

(108d) Et₃N (3.7 mL, 1.5 eq) and DPPA (4.6 mL, 1.2 eq) were added to a solution of the carboxylic acid from (108c) (5.12 g, 17.8 mmol) in benzene (150 mL). After 2 h at rt, benzyl alcohol (2.2 mL, 1.2 eq) was added. The mixture was heated to reflux for 1 h, cooled to rt, washed with sat NaHCO₃ (2 x 10 mL), brine (10 mL), dried (MgSO₄) and concentrated in vacuo. Silica gel chromatography (ethyl acetate-hexane, 20:80 then 30:70) provided the desired product (4.50 g, 64%). MS (M+H) +393.

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(108e) A mixture of the Cbz-protected intermediate from (108d) (2.30 g, 5.86 mmol) and Pd on carbon (0.60 g) in methanol (100 mL) was purged with hydrogen and stirred under balloon pressure hydrogen for 2 h. The catalyst was removed by filtration and the filtrate was concentrated to give the desired amine (1.52 g, 100%). MS (2M+H) =517.

(108f) Following the procedures similar to that used for step (100a), but using the amine from (108e) (1.35 g, 523 mmol), the amide was prepared. Silica gel chromatography (ethyl acetate-hexane, 50:50 then 60:40) provided the desired product (2.70 g, 85%). MS (M+H) = 534.

(108g) Following the procedures similar to that used for step (100b), the ester from (108f) (165 mg, 260 mmol) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product (85 mg, 52%). MS (M+H) +=521.

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Example 109

trans-N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-4pyrrolidinecarboxamide bis(trifluoroacetate)

(109a) The product from example 108 (50 mg, 0.079 mmol) was mixed with TFA (1 mL) and CH_2Cl_2 (2 mL) and stirred for 1 h. Concentration in vacuo provided the title compound (52 mg, 100%). MS $(M+H)^+=421$.

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Example 110

cis-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-3-[[[4[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4pyrrolidinecarboxamide trifluoroacetate

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(110a-b) Following the procedures similar to that used for steps (101a-b), the intermediate from (108f) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H)⁺=521.

Example 111

cis-N-hydroxy-3-[[[4-[(2-methyl-4-20 quinolinyl)methoxy]phenyl]carbonyl]amino]-4pyrrolidinecarboxamide bis(trifluoroacetate)

(111a) Following the procedure similar to that used for step (109a), the product from (110a) was converted to the title compound. MS (M+H) +=421.

Example 112

(3S, 4R)-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-4[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]3-piperidinecarboxamide trifluoroacetate

(112a) DIEA (82 mL, 2.5 eq) and (BOC)₂O (36.0 g, 1.3 eq) were added to a solution of methyl $4-\infty$ -3-piperidinecarboxylate (24.6 g, 137 mmol) in CH_2Cl_2 (600 mL) at 0°C. After at rt

overnight, sat $NaHCO_3$ (50 mL) was added. The mixture was washed with water (2x30 mL), brine (30 mL), dried (MgSO4) and concentrated in vacuo. Silica gel chromatography (ethyl acetate-hexane, 50:50) provided the desired product (29.8 g, 93%).

(112b) Yb(OTf)₃ (1.41 g, 0.02 eq) was added to a mixture of
the intermediate from (112a) (29.2 g, 113 mmol) and (R)-αmethylbenzylamine (16.1 mL, 1.1 eq) in benzene. The mixture

10 was heated to reflux for 3 h with azotropic removal of water
using a Dean-Stark trap. The mixture was concentrated in
vacuo. The residue was filtered through a silica gel pad and
the filter cake washed with ethyl acetate-hexane (10:90)
until free of product. The filtrated was concentrated to

15 give the desired enamine product (40.8 g, 100%). MS
(M+H)⁺=361.

(112c) NaHB(OAc)3 (58.8 g, 2.5 eq) was added to a solution of the enamine from (112b) (40.0 g, 111 mmol) in acetic acid (180 mL) and acetonitrile (180 mL) at 0°C. After 2 h at 0°C, the mixture was concentrated in vacuo. The residue was diluted with CH₂Cl₂ (1 L), washed with Na₂CO₃ (3x50 mL), brine (50 mL), dried (MgSO₄) and concentrated in vacuo. Silica gel chromatography (ethyl acetate-hexane, 10:90 then 20:80) provided the desired amine product as a 5:1 mixture of two diastereomers as judged by ¹H NMR (37.0 g, 92%). MS (M+H) +363.

(112d) Pd(OH)₂ on C (6.0 g) was added to the amine from (112c) (36.8 g, 101 mmol) in methanol (600 mL), water (60 mL) and acetic acid (15 mL). The mixture was purged with hydrogen and stirred under balloon pressure hydrogen overnight. Following removal of catalyst by filtration, the

filtrate was concentrated to give the desired amine (22.8 g, 87%). MS (M+H) +=259.

(112e) Following the procedure similar to that used for steps (100a), the amine from (112d) (10.0 g, 38.7 mmol) was coupled with 4-(2-methyl-4-quinolinylmethoxy)benzoic acid. Silica gel chromatography (ethyl acetate-hexane, 50:50 then 70:30) gave the desired amide (10.4 g, 50%). The enantiomeric purity of the amide was improved to >99% ee by crystallization with CHCl₃ (80 mL), ethyl acetate (10 mL) and hexane (10 mL). The material recovery from the crystalization was 63%. MS (M+H) =534.

(112f) Following the procedure similar to that used for steps (100b), the intermediate from (112e) (80 mg, 0.150 mmol) was converted to the hydroxamic acid. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acid product (43 mg, 44%). MS

20 (M+H) =535.

Example 113

(3S,4S)-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-4[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]3-piperidinecarboxamide trifluoroacetate

(113a-d) Following the procedures similar to that used for steps (112b-e), but using (S)- α -methylbenzylamine in step (112b), the (3R,4S) amide enantiomer was prepared. MS (M+H)⁺=534.

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(113e-f) Following the procedures similar to that used for steps (101a-b), the amide from (113d) was converted to the title compound. The product was purified by reverse phase

HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acid product. MS (M+H) +=535.

5 Example 114

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(3S, 4S) -N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide bis(trifluoroacetate)

10 (114a) Following the procedure similar to that used for step (109a), the product from (113f) was converted to the title compound. MS (M+H) +=435.

Example 115

15 (3S,4R)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide bis(trifluoroacetate)

(115a) Following the procedure similar to that used for step (109a), the product from (112f) was converted to the title compound. MS $(M+H)^+=435$.

Example 116

(3S, 4R) -1-[(butoxy)carbonyl]-N-hydroxy-4-[[[4-[(2-methyl-4-25 quinolinyl)methoxy]phenyl]carbonyl]amino]-3piperidinecarboxamide trifluoroacetate

(116a) Following the procedure similar to that used for step (109a), the intermediate from (112e) (2.24 g, 4.20 mmol) was converted to the desired amine bis-TFA salt (3.16 g, 100%).

MS (M+H) +=434.

(116b) DIEA (0.17 mL, 5 eq) and n-butyl chloroformate (30 mg, 1.1 eq) were added to the amine from (116a) (150 mg,

0.199 mmol) in CH_2Cl_2 . After 30 min at rt, ethyl acetate (100 mL) and sat NaHCO₃ (3 mL) were added. The mixture was washed with water (2x3 mL) and brine (3 mL), dried (MgSO₄) and concentrated in vacuo. The crude material was taken to the next step without further purification. $MS^-(M+H)^+=534$.

(116c) Following the procedures similar to that used for step (100b), the crude material from (116b) was converted to the title compound. The product was purified by reverse 10 phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acid product (38 mg, 29% for two steps). MS (M+H)⁺=535.

15 Example 117

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(3S, 4R)-N-hydroxy-1-[[(1-methylethyl)oxy]carbonyl]-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3piperidinecarboxamide trifluoroacetate

20 (117a-b) Following the procedures similar to that used for steps 116b and 100b, but with isopropyl chloroformate in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +521.

Example 118

(3S, 4R) -N-hydroxy-1-(methylsulfonyl)-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide trifluoroacetate

(118a-b) Following the procedures similar to that used for steps 116b and 100b, but with MsCl in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an

acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=513.

Example 119

(3S, 4R) -N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(phenylsulfonyl)-3-piperidinecarboxamide trifluoroacetate

(119a-b) Following the procedures similar to that used for steps 116b and 100b, but with benzenesulfonyl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=575.

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Example 120

(3S, 4R) -1-acetyl-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide trifluoroacetate

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(120a-b) Following the procedures similar to that used for steps 116b and 100b, but with acetic anhydride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=477.

Example 121

(3S, 4R)-1-benzoyl-N-hydroxy-4-[[[4-[(2-methyl-4-30 quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide trifluoroacetate

(121a-b) Following the procedures similar to that used for steps 116b and 100b, but with benzoyl chloride in step (116b), the title compound was prepared. The product was

purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=539.

5 Example 122

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(3S, 4R)-1-(2,2-dimethylpripionyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide trifluoroacetate

10 (122a-b) Following the procedures similar to that used for steps 116b and 100b, but with trimethylacetyl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=519.

Example 123

(3S,4R)-1-(3,3-dimethylbutanoyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide trifluoroacetate

(123a-b) Following the procedures similar to that used for steps 116b and 100b, but with 3,3-dimethylbutyryl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=533.

Example 124

30 (3S, 4R) -N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(4-morpholinecarbonyl)-3-piperidinecarboxamide trifluoroacetate

(124a-b) Following the procedures similar to that used for steps 116b and 100b, but with 4-morpholinecarbonyl chloride

in step (116b), the title compound was prepared. The product—was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +548.

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Example 125

(3S, 4R)-1-(dimethylcarbamyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide trifluoroacetate

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(125a-b) Following the procedures similar to that used for steps 116b and 100b, but with dimethylcarbamyl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=506.

Example 126

(3S, 4R) -N-hydroxy-1-methyl-4-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-3piperidinecarboxamide bis(trifluoroacetate)

(126a) DIEA (0.23 mL, 5 eq) and 37% aqueous formaldehyde (24 mg, 1.1 eq) were added to the amine intermediate from (116a) (200 mg, 0.258 mmol) in 1,2-dichloroethane (6 mL). After 30 min at rt, NaHB(OAc)₃ (82 mg, 1.5 eq) was added. After additional 1 h at rt, sat NaHCO₃ (3 mL) and ethyl acetate (100 mL) were added. The mixture was washed with water (2x5 mL) and brine (5 mL), dried (MgSO₄) and concentrated in vacuo. The crude material was used in the next step without further purification. MS (M+H) +=448.

(126b) Following the procedures similar to that used for step (100b), the crude intermediate from (126a) was converted to the title compound. The product was purified by

reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acid (50 mg, 32% for two steps). MS (M+H) +=449.

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Example 127

(3S, 4R) -1-ethyl-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide bis(trifluoroacetate)

10 (127a-b) Following the procedures similar to that used for steps 126a and 100b, but with acetaldehdye in step (126b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=463.

Example 128

(3S, 4R) -N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-propyl-3-piperidinecarboxamide bis(trifluoroacetate)

(128a-b) Following the procedures similar to that used for steps 126a and 100b, but with propional dehyde in step (126b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +477.

Example 129

30 (3S, 4R) -N-hydroxy-1-(1-methylethyl) -4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide bis(trifluoroacetate)

(129a-b) Following the procedures similar to that used for steps 126a and 100b, but with acetone in step (126b), the

title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=477.

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Example 130

(3S, 4R)-1-(cyclopropylmethyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide bis(trifluoroacetate)

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(130a-b) Following the procedures similar to that used for steps 126a and 100b, but with cyclopropanecarboxaldehyde in step (126b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=489.

Example 131

(3S, 4R)-1-(2,2-dimethylpropyl)-N-hydroxy-4-[[[4-[(2-methyl-20 4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide bis(trifluoroacetate)

(131a-b) Following the procedures similar to that used for steps 126a and 100b, but with trimethylacetaldehyde in step (126b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) =505.

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Example 132

(3S, 4R)-1-benzyl-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide bis(trifluoroacetate)

(132a-b) Following the procedures similar to that used for steps 126a and 100b, but with benzaldehyde in step (126b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H)⁺=525.

Example 133

(3S, 4R)-1-(2-thiazolylmethyl)-N-hydroxy-4-[[[4-[(2-methyl-4-10 quinolinyl)methoxy]phenyl]carbonyl]amino]-3piperidinecarboxamide bis(trifluoroacetate)

(133a-b) Following the procedures similar to that used for steps 126a and 100b, but with 2-thiazolecarboxaldehyde in step (126b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H)⁺=532.

20 Example 134

(3S,4S)-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide trifluoroacetate

25 (134a). A mixture of ethyl 1-benzyl-3-oxo-4piperidinecarboxylate hydrochloride (50 g, 168 mmol), (BOC)₂O
(50 g, 1.36 eq), Et₃N (35.2 mL, 1.5 eq), Pd(OH)₂ on C (10 g)
and ethanol (400 mL) was hydrogenated at 50 psi overnight.
Following removal of catalyst by filtration, the filtrate
30 was concentrated, diluted with ethyl acetate (1 L), washed
with 0.5 N HCl (300 mL), sat NaHCO₃ (150 mL), brine (100 mL),
dried (MgSO₄) and concentrated in vacuo. Silica gel
chromatography (ethyl acetate-hexane, 5:95 then 10:90)
provided the desired product (39.0 g, 86%). MS (M+H)⁺=272.

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(134b-e) Following the procedures similar to that used for steps (112b-e), the intermediate from (134a) was converted to the desired amide. The material obtained through this route was 40% ee as determined by analytical chiral HPLC. The enantiomeric purity of the major enantiomer was improved to >99% ee using preparative chiral HPLC. The minor enantiomer was also collected. MS (M+H) +548.

(134f) Following the procedures similar to that used for step (100b), the major enantiomer from (134e) (100 mg, 0.180 mmol) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acid product (83.5 mg, 72%). MS

15 (M+H) +=535.

Example 135

(3R,4S)-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-3- [[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]- 4-piperidimecarboxamide trifluoroacetate

(135a-b) Following the procedures similar to that used for steps (101a-b), the minor enantiomer from (134e) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=535.

Example 136

30 (3R,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

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(136a) Following the procedure similar to that used for step (109a), the product from (135b) was converted to the title compound. MS $(M+H)^+=435$.

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Example 137

(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

10 (137a) Following the procedure similar to that used for step (109a), the product from (134f) was converted to the title compound. MS (M+H) +=435.

Example 138

- 15 (3S,4S)-N-hydroxy-1-[[(2-methylpropyl)oxy]carbonyl]-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide trifluoroacetate
- (138a) Following the procedure similar to that used for step (109a), the major enantiomer from (134e) (500 mg, 0.913 mmol) was converted to the desired amine bis-TFA salt (616 mg, 100%). MS (M+H) +=448.
- (138b-c) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (138a) and isobutyl chloroformate in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=535.

Example 139

(3S, 4S) -N-hydroxy-1-(methoxycarbonyl)-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide trifluoroacetate

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(139a-b) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (138a) and methyl chloroformate in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=493.

Example 140

15 (3S,4S)-N-hydroxy-1-[(1-methylethoxy)carbonyl]-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide trifluoroacetate

(140a-b) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (138a) and isopropyl chloroformate in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=521.

Example 141

(3S,4S)-N-hydroxy-1-(methylsulfonyl)-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide trifluoroacetate

(141a-b) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (138a) and methanesulfonyl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC

on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +513.

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Example 142

(3S, 4S) -N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(phenylsulfonyl)-4-piperidinecarboxamide trifluoroacetate

- 10 (142a-b) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (138a) and benzenesulfonyl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an
- acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) += 575.

Example 147

(3S,4S)-1-(3,3-dimethylbutanoyl)-N-hydroxy-3-[[[4-[(2-20 methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide trifluoroacetate

(147a-b) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (138a) and t-butylacetyl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=533.

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Example 148

(3S, 4S) -1-(2, 2-dimethylpropionyl) -N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide trifluoroacetate

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(148a-b) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (138a) and trimethylacetyl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +519.

Example 149

10 (3S,4S)-1-benzoyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide trifluoroacetate

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(149a-b) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (138a) and benzoyl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=539.

Example 150

(3S, 4S) -1-[(pyridin-3-yl)carbonyl]-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

(150a-b) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (138a) and nicotinoyl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=540.

Example 151

(3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 - 1)]]]]quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(2thiophenecarbonyl)-4-piperidinecarboxamide trifluoroacetate

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(151a-b) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (138a) and 2thiophenecarbonyl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS $(M+H)^+=545$.

Example 152

15 (3S, 4S) - 1 - (dimethylcarbamyl) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 - mquinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide trifluoroacetate

(152a-b) Following the procedures similar to that used for 20 steps 116b and 100b, but with the amine from (138a) and dimethylcarbamyl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS $(M+H)^{+}=506$.

Example 153

(3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(4morpholinecarbonyl)-4-piperidinecarboxamide trifluoroacetate

(153a-b) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (138a) and 4morpholinecarbonyl chloride in step (116b), the title compound was prepared. The product was purified by reverse

phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=548.

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Example 154

(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-[[2-(2-thienyl)ethyl]carbamyl]-4-piperidinecarboxamide trifluoroacetate

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(154a-b) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (138a) and 2-(thien-2-yl)ethyl isocyanate in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +588.

Example 155

20 (3S,4S)-1-[(1,1-dimethylethyl)carbamyl]-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide trifluoroacetate

(155a-b) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (138a) and t-butyl isocyanate in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=534.

Example 156

(3S,4S)-N-hydroxy-1-methyl-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

(156a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and para-formaldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H)⁺=449.

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Example 157

(3S, 4S) -1-ethyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

- 15 (157a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and acetaldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an
- 20 acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=463.

Example 158

(3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 -

quinolinyl)methoxy]phenyl]carbonyl]amino]-1-propyl-4piperidinecarboxamide bis(trifluoroacetate)

(158a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and propionaldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=477.

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Example 159

(3S, 4S) -N-hydroxy-1-(1-methylethyl)-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

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(159a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and acetone in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +477.

Example 160

(3S,4S)-1-cyclobutyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

(160a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and cyclobutanone in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=489.

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Example 161

(3S, 4S) -1-butyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

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(161a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and butyraldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an

acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=491.

Example 162

5 (3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(2-methylpropyl)-4-piperidinecarboxamide bis(trifluoroacetate)

(162a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and isobutyraldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=491.

Example 163

(3S, 4S)-1-(cyclopropylmethyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

(163a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and cyclopropanecarboxaldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=489.

30 Example 164

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(3S, 4S)-1-(2, 2-dimethylpropyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

(164a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and trimethylacetaldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=505.

Example 165

10 (3S, 4S)-1-cyclopentyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

(165a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and cyclopentanone in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=503.

Example 166

(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(4-tetrahydropyranyl)-4-piperidinecarboxamide bis(trifluoroacetate)

(166a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and tetrahydro-4H-pyran-4-one in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=519.

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Example 167-

(3S, 4S)-1-benzyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

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(167a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and benzaldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=525.

Example 168

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(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(2-thiazolylmethyl)-4-piperidinecarboxamide bis(trifluoroacetate)

- 20 (168a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and 2-thiazolecarboxaldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an
- 25 acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=532.

Example 169

(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(4pyridinylmethyl)-4-piperidinecarboxamide
bis(trifluoroacetate)

(169a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and 4-

pyridinecarboxaldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H)⁺=526.

Example 170

(3S, 4S) -N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(2-pyridinylmethyl)-4-piperidinecarboxamide
bis(trifluoroacetate)

(170a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and 2-pyridinecarboxaldehyde in step*(126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H)*=526.

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Example 171

(3S, 4S) -N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(3pyridinylmethyl)-4-piperidinecarboxamide
bis(trifluoroacetate)

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(171a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and 3-pyridinecarboxaldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=526.

Example 172

(3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 -

quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(trans-3-phenyl-2-propenyl)-4-piperidinecarboxamide bis(trifluoroacetate)

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(172a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (138a) and trans-cinnamaldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=551.

Example 173

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(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-1-phenyl-4piperidinecarboxamide bis(trifluoroacetate)

(173a) A mixture of the amine from (138a) (100 mg, 0.223

20 mmol, free base), benzeneboronic acid (54.5 mg, 2 eq), copper (II) acetate monohydrate (133.8 mg, 3 eq), pyridine (0.054 mL, 3 eq), 4 A molecular sieve (165 mg) and CH₂Cl₂ (2 mL) were stirred overnight with the flask open to the atmosphere. The mixture was filtered and the filtrate

25 concentrated in vacuo. Silica gel chromatography (ethyl acetate-hexane, 60:40 then 70:30) provided the desired product (94 mg, 80%). MS (M+H) +524.

(173b) Following the procedures similar to that used for step (100b), the intermediate from (173a) (94 mg, 0.180 mmol) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acid (74 mg, 56%). MS (M+H) *=511.

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Example 174.

(3R, 4S)-1-(2, 2-dimethylpropionyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide trifluoroacetate

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(174a-b) Following the procedures similar to that used for steps 101a and 109a, the minor enantiomer from (134e) was epimerized with DBU and deprotected. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the trans isomer. MS (M+H) +=448.

(174c-d) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (174b) and trimethylacetyl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acid. MS (M+H) +=519.

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Example 175

(3R, 4S) -N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-methyl-4-piperidinecarboxamide bis(trifluoroacetate)

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(175a-b) Following the procedures similar to that used for steps 126a and 100b, but with the amine from (174b) and para-formaldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H)⁺=449.

Example 176

(3R, 4S)-1-(dimethylcarbamyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide trifluoroacetate

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(176a-b) Following the procedures similar to that used for steps 116b and 100b, but with the amine from (174b) and dimethylcarbamyl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +506.

Example 177

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(3S, 4S) -1-hexyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

(177a-b) Following the procedures similar to that used for steps 126a and 100b, but using the amine from (138a) and hexanal in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS

25 $(M+H)^+=519$.

Example 178

(3S, 4S) -1-(2-fluoroethyl) -N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

(178a) A mixture of the amine from (138a) (800 mg, 1.20 mmol), 1-bromo-2-fluoroehtane (0.27 mL), 3 eq), K_2CO_3 (1.20 g, 10 eq) and NaI (580 mg, 3 eq) in acetone (20 mL) was

heated to reflux for 6 h, cooled to rt and filtered. The filtrate was concentrated and purified by silica gel chromatography (methanol-dichloromethane, 5:95) to give the desired product (450 mg, 76%). MS (M+H) +=538.

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(178b) Following the procedures similar to that used for step (100b), the intermediate from (178a) (350 mg, 0.710 mmol) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acid (170 mg, 34%). MS (M+H) +=481.

Example 179

(3S,4S)-1-(2,2-difluoroethyl)-N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide bis(trifluoroacetate)

(179a-b) Following the procedures similar to that used for steps (178a and 100b), but the amine from (138a) and 2-bromo-1,1-diffluoroethane in step (178a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=499.

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Example 180

(3S, 4S) -N-hydroxy-1-(1-methylpropyl)-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

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(180a-b) Following the procedures similar to that used for steps (126a and 100b), but using the amine from (138a) and 2-butanone in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-

18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS

(M+H) +=491.

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Example 181

(3S, 4S)-1-(1-ethylpropyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

10 (181a-b) Following the procedures similar to that used for steps (126a and 100b), but using the amine from (138a) and 3-pentanone in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=505.

Example 182

(3S,4S)-1-[1-[[(1,1-dimethylethyl)oxy]carbonyl]-420 tetrahydropiperidinyl]-N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide bis(trifluoroacetate)

(182a-b) Following the procedures similar to that used for steps (126a and 100b), but using the amine from (138a) and Boc-4-piperidone in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=618.

Example 183

(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(4-

tetrahydropiperidinyl)-4-piperidinecarboxamide tris(trifluoroacetate)

(183a) Following the procedure similar to that used for step (109a), the product from (182b) was converted to the title compound. MS (M+H) +=518.

Example 184

(3S,4S)-1-[1-[[(1,1-dimethylethyl)oxy]carbonyl]-3
tetrahydropyrrolidinyl]-N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide bis(trifluoroacetate)

(184a-b) Following the procedures similar to that used for steps (126a and 100b), but using the amine from (138a) and N-Boc-3-pyrrolidinone in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=604.

Example 185

(3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(3-tetrahydropyrrolidinyl)-4-piperidinecarboxamide tris(trifluoroacetate)

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(185a) Following the procedure similar to that used for step (109a), the product from (184b) was converted to the title 30 compound. MS (M+H) +=505.

Example 186

(3S, 4S) -1-(1, 1-dimethyl-2-propynyl) -N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

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(186a) A solution of 3-chloro-3-methyl-1-butyne (0.51 ml, 1 eq) in dichloromethane (2 mL) was added dropwise to a mixture of the amine from (138a) (2.00 g, 4.47 mmol), CuCl (1 mg), Cu (1 mg), Et₃N (1.30 mL, 2 eq), water (15 mL) and dichloromethane (30 mL). After stirring under N₂ for 4 days, the mixture was diluted with dichloromethane and water. The organic phase was separated and purified by silica gel chromatography (methanol-dichloromethane, 5:95) to give the desired product (1.76 g, 76%). MS (M+H) +514.

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(186b) Following the procedures similar to that used for step (100b), the intermediate from (186a) (200 mg, 0.389 mmol) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acid (95 mg, 33%). MS (M+H) +=501.

Example 187

(3S, 4S) -N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(3thiophenylmethyl)-4-piperidinecarboxamide
bis(trifluoroacetate)

(187a-b) Following the procedures similar to that used for steps (126a and 100b), but using the amine from (138a) and 3-thiophenecarboxaldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an

acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=531.

Example 188

5 (3S, 4S) -N-hydroxy-1-(1-methylethyl)-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-oxo-4-piperidinecarboxamide trifluoroacetate

(188a) Following the procedures similar to that used for steps (126a), but using the amine from (138a) (4.00 g, 5.92 mmol) and acetone, the title compound was prepared. Silica gel chromatography (methanol-dichloromethane, 5:95 then 7:93) gave the desired product (2.36 g, 81%). MS (M+H) +=490.

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(188b) m-CPBA (102 mg, 1 eq, 55% pure) was added to a solution of the tert-amine from (188a) (160 mg, 0.327 mmol) in dichloromethane (4 mL). After 30 min at rt, the mixture was treated with saturated NaHSO₃ (1.5 mL) and saturated NaHCO₃ (1.5 mL), and immediately extracted with ethyl acetate. The extracts were washed with brine, dried and concentrated (MgSO₄). Silica gel chromatography (methanol-dichloromethane, 5:95 then 10:90) gave the tertiary amine Noxide (140 mg, 85%). MS (M+H) +506.

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(188c) Following the procedures similar to that used for step (100b), the intermediate from (188b) (30 mg, 0.059 mmol) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acid (25 mg, 69%). MS (M+H) +=493.

Example 189

(3S, 4S) -N-hydroxy-1-(1-methylethyl)-3-[[[4-[(2-methyl-1-oxo-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide trifluoroacetate

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(189a) The momo-N-oxide from (188b) (110 mg, 0.218 mmol) was dissolved in dichloromethane (2 mL) and treated with m-CPBA (68.3 mg, 1 eq, 55% pure) for 30 min. TLC showed clean conversion to the bis-N-oxide product. The mixture was treated with saturated NaHSO3 (1.5 mL) and saturated NaHCO3 (1.5 mL), and extracted with ethyl acetate. The NaHSO3 treatment resulted in partial reduction of the tertiary amine N-oxide and therefore gave a mixture of bis-N-oxide and quinoline mono-N-oxide. The extracts were washed with brine, dried and concentrated (MgSO4). Silica gel chromatography (methanol-dichloromethane, 5:95 then 8:92 then 10:90 then 15:85) gave the mono-N-oxide at the quinoline nitrogen (50 mg, 44%) and bis-N-oxide (40 mg, 35%). MS for mono-N-oxide (M+H) +=506, for bis-N-oxide (M+H) +=522.

(189b) Following the procedures similar to that used for step (100b), the mono-N-oxide from (189a) (48 mg, 0.095 mmol) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acid (30 mg, 52%). MS (M+H) +=493.

Example 190

30 (3S,4S)-N-hydroxy-1-(1-methylethyl)-3-[[[4-[(2-methyl-1-oxo-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-oxo-4-piperidinecarboxamide

(190a) Following the procedures similar to that used for step (100b), the bis-N-oxide from (189a) (38 mg, 0.073 mmol) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acid (23 mg, 62%). MS (M+H) +=509.

Example 191

(3S, 4S) -N-hydroxy-3-[[[4-[(2-methyl-4-10 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-[2-(4morpholinyl)-2-oxoethyl]-4-piperidinecarboxamide bis(trifluoroacetate)

(191a) A mixture of the amine from (138a) (2.00 g, 2.96

15 mmol), t-butyl bromoacetate (1.15 g, 2 eq), Cs2CO3 (4.82 g, 5 eq) and DMSO (25 mL) was stirred at rt for 1 h. Following addition of sat NH₄Cl (15 mL) and ethyl acetate (200 mL), the mixture was washed with water (2x10 mL), brine (10 mL), dried (MgSO₄) and concentrated. Silica gel chromatography

20 (ethyl acetate) provided the desired product (1.40 g, 80%).

MS (M+H) +=562.

(191b) The t-butyl eater from (191a) (1.20 g, 2.14 mmol) was treated with TFA (5 mL) in dichloromethane (5 mL) for 3 h and concentrated to give the desired carboxylic acid (1.70 g, 100%). MS (M+H) +=506.

(191c) Following the procedure similar to that used for steps (100a), The acid from (191b) (300 mg, 0.378 mmol) was coupled with morpholine. Silica gel chromatography (methanol-dichloromethane, 5:95) gave the desired amide (130 mg, 59%). MS (M+H) +=575.

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(191d) Following the procedures similar to that used for step (100b), the product from (191c) (130 mg, 0.223 mmol) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acid (70 mg, 53%). MS (M+H) +=562.

Example 192

(3S,4S)-1-[2-(N,N-dimethylamino)-2-oxoethyl]-N-hydroxy-3
[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]
4-piperidinecarboxamide bis(trifluoroacetate)

(192a-b) Following the procedures similar to that used for steps (100a-b), but using the acid from (191b) and dimethylamine in step (100a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=520.

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Example 193

(3S,4S)-1-(t-butylsulfonyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide trifluoroacetate

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(193a) A precooled solution (0 oC) of t-Butylsulfinyl chloride (210 mg, 2 eq) in dichloromethane (10 mL) was added dropwise to a solution of triethylamine (1.03 mL, 10 eq) and the amine from (138a) (500 mg, 0.74 mmol) in dichloromethane (10 mL) at 0 oC. After 1 h at 0°C, the mixture was quenched with sat NaHCO₃ and extracted with dichloromethane. The extracts were dried (MgSO₄) and concentrated. Silica gel chromatography (methanol-dichloromethane, 5:95) gave the

desired sulfinamide (400 mg, 98%) as a 1:1 mixture epimeric at sulfur center. MS $(M+H)^+=552$.

(193b) Ruthenium(III) chloride monohydrate (0.4 mg) and NaIO₄ (46 mg, 1.2 eq) were added to a mixture of the sulfinamide from (193a) (100 mg, 0.180 mmol), dichloromethane (2 mL), acetonitrile (2 mL) and water (3 mL) at 0 oC. After 1 h at 0 oC, the mixture was extracted with dichloromethane. The combined extracts were dried (MgSO₄) and concentrated to give the desired sulfonamide as a crude material. MS (M+H) +=568.

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(193c) Following the procedures similar to that used for step (100b), the crude product from (193b) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acid (47 mg, 39% for two steps). MS (M+H) +=555.

Example 194

20 (3S,4S)-1-(t-butylsulfonyl)-N-hydroxy-3-[[[4-[(2-methyl-1-oxo-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide

(194a) Following a procedure similar to that used for step (189a), the sulfinamide from (193a) (220 mg, 0.400 mmol) was oxidized to the sulfonamide quinoline N-oxide (250 mg crude weight). MS (M+H) +=584.

(194b) Following the procedures similar to that used for step (100b), the crude product from (194a) (100 mg) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the

desired hydroxamic acid (64 mg, 65% for two steps). MS $(M+H)^+=571$.

Example 195

5 (35,45)-1-(benzenesulfonyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide trifluoroacetate

(195a-b) Following the procedures similar to that used for steps (116b and 100b), but using the amine from (138a) and benzenesulfonyl chloride in step (116b), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=575.

Example 196

(3S, 4S)-1-(t-butylsulfinyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide trifluoroacetate

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(196a) Following the procedures similar to that used for step (100b), the 1:1 mixture of sulfinamide from (193a) was converted to the title compound. The two isomers were separated by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the desired hydroxamic acids. MS (M+H) +=539.

Example 197

30 (3S,4S)-N-hydroxy-1-(2-hydroxylethyl)-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide bis(trifluoroacetate)

(197a) Following the procedure similar to that used for step (126a), the amine from (138a) (225 mg, 0.333 mmol) was reacted with (t-butyldimethylsilyloxy)acetaldehyde via reductive amination. Silica gel chromatography (ethyl acetate-hexane, 30:70, then methanol-dichloromethane, 5:95) gave the desired product (150 mg, 74%) MS (M+H)+=606.

(197b) A 1 M THF solution of TBAF (0.50 mL, 2 eq) was added to the product from (197a) (150 mg, 0.248 mmol) in THF (6 mL). The mixture was stirred for 30 min, diluted with sat NH₄Cl (5 mL) and ethyl acetate (100 mL), washed with water (5 mL), brine (5 mL), dried (MgSO₄) and concentrated. Silica gel chromatography (methanol-dichloromethane, 5:95) gave the desired alcohol (100 mg, 82%). MS (M+H) +=492.

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(197c) Following the procedures similar to that used for step (100b), the product from (197b) (100 mg, 0.203 mmol) was converted to the title compound. Purification by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, gave the desired hydroxamic acid (35 mg, 24%). MS (M+H) +=479.

Example 198

(3S, 4S) - 1 - [2 - [[[(1, 1 -

25 dimethylethyl)oxy]carbonyl]amino]ethyl]-N-hydroxy-3-[[[4[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide bis(trifluoroacetate)

(198a) Following the procedure similar to that used for step (126a), the amine from (138a) (200 mg, 0.296 mmol) was reacted with t-butyl N-(2-oxoethyl)carbamate via reductive amination. Silica gel chromatography (methanol-dichloromethane, 5:95) gave the desired product (150 mg, 86%). MS (M+H) +=591.

(198b) Following the procedures similar to that used for step (100b), the product from (198a) (120-mg, 0.203 mmol) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product (80 mg, 49%). MS (M+H) +578.

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Example 199

10 (3S,4S)-1-(2-aminoethyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide tris(trifluoroacetate)

(199a) Following the procedure similar to that used for step (109a), the product from (198b) was converted to the title compound. MS (M+H) +=478.

Example 200

(3S,4S)-1-[2-(N,N-dimethylamino)ethyl]-N-hydroxy-3-[[[4-[(2-20 methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide tris(trifluoroacetate)

(200a) Following the procedure similar to that used for step (109a), the product from (198a) (380 mg, 0.643 mmol) was deprotected to give the desired product (550 mg, 100%). MS (M+H) +=491.

(200b) Following the procedure similar to that used for step (126a), the amine from (200a) (300 mg, 0.351 mmol) was reacted with formaldehyde via reductive amination. Silica gel chromatography (methanol-dichloromethane-ammonium hydroxide, 10:90:0 then 10:88:2) gave the dimethylamino product (160 mg, 88%). MS (M+H) +=519.

(200c) Following the procedure similar to that used for step (100b), the product from (200b) (150 mg, 0.289 mmol) was converted to the title compound. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product (140 mg, 57%). MS (M+H) +=506.

Example 201

(3S,4S)-1-[(2S)-2-aminopropyl]-N-hydroxy-3-[[[4-[(2-methyl-10 4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide tris(trifluoroacetate)

(201a-c) Following the procedures similar to that used for steps (126a, 100b and 109a), but using the amine from (138a) and N-t-Boc-L-alaninal in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=492.

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Example 202

(3S, 4S)-1-[(2R)-2-amino-3-hydroxypropyl]-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide tris(trifluoroacetate)

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(202a-c) Following the procedures similar to that used for steps (126a, 100b and 109a), but using the amine from (138a) and S-(-)-3-tert-butoxycarbonyl-4-formyl-2,2-dimethyl-1,3-oxazolidine in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +508.

Example 203 -

(203a-c) Following the procedures similar to that used for steps (126a, 100b and 109a), but using the amine from (138a) and N-(tert-butoxycarbonyl)-D-prolinal in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=518.

15 Example 204

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(3S, 4R) -N-hydroxy-1-(2-hydroxylethyl)-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide bis(trifluoroacetate)

20 (204a-c) Following the procedures similar to that used for steps (126a, 197b and 100b), but using the amine from (116a) and (t-butyldimethylsilyloxy)acetaldehyde in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=479.

Example 205

(3S,4R)-1-(2-aminoethyl)-N-hydroxy-4-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-3piperidinecarboxamide tris(trifluoroacetate)

(205a-c) Following the procedures similar to that used for steps (126a, 100b and 109a), but using the amine from (116a)

and t-butyl N-(2-oxoethyl)carbamate in step (126a), the title compound was prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) +=478.

Example 206

(3S, 4R) -1-cyclobutyl-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide bis(trifluoroacetate)

(206a-b) Following the procedures similar to that used for steps (126a and 100b), but using the amine from (116a) and cyclobutanone in step (126a), the title compound was

15 prepared. The product was purified by reverse phase HPLC on a Vydac C-18 semiprep column eluting an acetonitrile:water:TFA gradient, to give the hydroxamic acid product. MS (M+H) + 489.

20 Example 207

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(3R, 4R) - N-hydroxy-4- $(\{4-[(2-methyl-4-quinolinyl)methoxy]benzoyl\}amino)tetrahydro-<math>2H$ -pyran-3-carboxamide

25 (207a) LiHMDS (1.0 M in THF, 52.5 mL, 1.05 eq) was added dropwise to a -78°C solution of tetrahydro-4H-pyran-4-one (5.0 g, 50 mmol) in THF (200 mL). The resulting solution was stirred at -20°C for 1 h, then cooled back to -78°C. To this mixture was added methyl cyanoformate (4.75 mL, 1.2 eq) dropwise. Ten min after completion of the addition, the reaction was quenched with aqueous NH₄Cl and extracted with ether (200 mL). The organic layer was washed with brine (100 mL), dried (MgSO₄), and concentrated. Silica gel column chromatography (ether-hexane, 1:4, 2:3, then 3:2) yielded an

oil containing both ketone and enol forms of the product (5.4 g, ca. 30 % purity). MS found: (M+H) + = 159.1.

(207b) The ester from (207a) was dissolved in benzene (200 mL) and treated with (R)-α-methylbenzylamine (3 mL) and ytterbium(III) trifluoromethanesulfonate (200 mg). The mixture was heated to reflux under Dean-Stark conditions for 2 h, concentrated, and purified by silica gel column chromatography (ethyl acatete-hexane, 1:4) to yield the desired enamine as a white solid (3.6 g, 27.5% for 2 steps).

(207c) The enamine from (207b) (3.5 g, 13.4 mmol) in acetonitrile-acetic acid (1:1, 80 mL) was treated with NaBH(OAc)₃ and stirred for 2 h at 0 °C. Following 15 concentration in vacuo, the residue was dissolved in ether (200 mL), washed with saturated NaHCO₃ until the aqueous phase was basic, dried (MgSO₄), and concentrated to yield an oil (3.39 g, 96%). MS Found: (M+H)⁺ = 264.3.

(207d) The intermediate from (207c) (1.86 g, 7.06 mmol) in methanol (100 mL) was treated with 10% palladium hydroxide on carbon (0.6 g, 3.5 % mol) and aqueous 1N hydrochloric acid (10 mL, 1.4 eq) and stirred under a H₂-balloon for 72 h. The catalyst was removed by filtration. Removal of solvent provided the desired amine as hydrochloric acid salt (1.42 g, 100%). MS Found: (M+H)⁺ = 160.3.

(207e) To a mixture of the amine from (207d) (1.0 g, 5.11 mmol) and 4-[(2-methyl-4-quinolinyl)methoxy]benzoic acid

(1.50 g, 1.0 eq) in N,N-dimethylformamide (20 ml) was added BOP reagent (2.30 g, 1.02 eq) and N,N-diisopropylethylamine (2.2 mL, 2.5 eq) at room temperature. After 2 h at room temperature, saturated aqueous NaHCO3 (50 ml) was added and the mixture extracted with ethyl acetate (2 x 50 mL), washed with brine (20 mL), dried (MgSO4) and concentrated. Silica

gel column chromatography (ethyl acetate-hexane, 3:2 then 4:1) yielded the desired amide (1.6 g, 72%). The above amide was submitted for a chiral HPLC separation (OJ, hexane-isopropanol-methanol, 60:20:20, 1.2 mL/min @ 240 nM and ambient temperature) to provide the (3R,4R) isomer in enantiomerically pure form (980 mg, 58% recovery, >99% ee). MS Found: $(M+H)^+ = 435.1$.

(207f) Freshly prepared 1.76 M hydroxylamine solution

(example 1d) (20 mL, 20 eq.) was added to the methyl ester
(0.78 g, 1.80 mmol) from reaction (207e) and stirred at room
temperature for 10 min. The mixture was adjusted to pH 7
with 1 N hydrochloric acid. The resulting precipitate was
collected by filtration and recrystallized from hot methanol

(80 mL) to yield the free base form of the hydroxamic acid.
The free base was treated with dichloromethane (30 mL) and
trifluoroacetic acid (0.1 mL, 1.5 eq) and stirred until
homogeneous. The mixture was concentrated and lyophilized
to afford the TFA salt of the desired hydroxamic acid (0.50

g, 50%). MS Found: (M+H) + = 436.1.

Example 208

(3S,4S)-1-tert-butyl-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4-piperidinecarboxamide bis(trifluoroacetate)

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(208a) To a solution of the alcohol (0.95 g, 3.09 mmol) from reaction (222a) in dichloromethane (30 mL) was added, at 0°C, triethylamine (0.65 mL, 1.5 eq), and methanesulfonyl chloride (0.29 mL, 1.2 eq). After 15 min at 0°C, the reaction was quenched with saturated NaHCO₃ (10 mL), extracted with dichloromethane, washed with brine, dried (MgSO₄), concentrated and purified by silica gel chromatography (40% then 50% ethyl acetate/hexane) to yield the mesylate (0.99 g, 83%). MS found: (M+Na)+408.

(208b) To a -78°C solution of the mesylate (0.90 g, 2.33 mmol) from reaction (208a) in dichloromethane (100 mL) was bubbled ozone until the reaction solution turned blue. The reaction was purged with nitrogen until colorless. Triphenylphosphine (0.73 g, 1.2 eq) was added, and the mixture was stirred at ambient temperature for 2 h, concentrated and purified by silica gel chromatography (60% ethyl acetate/hexane) to yield the desired aldehyde (0.81 g, 90%). MS found: (M+Na)*=410.

(208c) A mixture of the aldehyde (0.81 mg, 2.09 mmol) from the reaction (208b), tert-butylamine (1.14 mL, 5.2 eq) and sodium triacetoxyborohydride (1.33 g, 3.0 eq) in

15 dichloroethane (40 mL) was stirred in a sealed flask at room temperature for 4 h, then 80°C overnight. The reaction was quenched with saturated NaHCO₃, extracted with dichloromethane (2x50 mL), washed with brine (50 mL), dried (MgSO₄), concentrated and purified twice by silica gel

20 chromatography (60% ethyl acetate/hexane) to yield the desired cyclized tertiary amine (0.37 g, 40%). MS found: (M+H) +349.

(208d) A mixture of the amine (0.32 g, 0.92 mmol) from
25 reaction (208c), Pd/C (64 mg, 20% wt) and 1 N hydrogen
chloride in ethyl ether (1.0 mL) in methanol (20 mL) was
stirred under a hydrogen-balloon for 1 h. After removal of
catalyst by filtration, the filtrate was concentrated to
afford the deprotected amine hydrochloride (0.23 g, 100%).

30 MS found: $(M+H)^{+}=215$.

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(208e) Following a procedure analogous to that used in reaction (16f), the amine hydrochloride (0.23g, 0.92 mmol) from reaction (208d) was coupled with 4-(2-methyl-4-quinolinylmethoxy)benzoic acid. Silica gel chromatography

(3% methanol/dichloromethane) provided the desired amide (0.37 g, 82%). MS found: $(M+H)^{+}=490$.

(208f) Following a procedure analogous to that used in reaction (1d), the methyl ester (0.25 g, 0.51 mmol) from reaction (208e) was treated with hydroxylamine solution. Purification by reverse phase HPLC (15-40% acetonitrile/water) yielded the desired hydroxamic acid (0.26 g, 71%). MS found: (M+H) +491.

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Example 209

tert-butyl 2-[(3S,4S)-4-[(hydroxyamino)carbonyl]-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl)amino)piperidinyl]-2-methylpropanoate bis(trifluoroacetate)

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- (209a) The amine from reaction (138a) (250 mg, 0.370 mmol), tert-butyl 2-bromoisobutyrate (0.69 mL, 10 eq) and potassium carbonate (760 mg, 15 eq) were added to acetone (20 mL) and heated to reflux for 24 h. The mixture was cooled to rt and concentrated in vacuo. Purification of the residue by silica gel column chromatography (5:95, methanol:methylene chloride) gave the desired tertiary amine (50 mg, 23%). MS found: (M+H) +=590.
- (209b) Following a procedure similar to that used for reaction (100b), the tertiary amine from reaction (209a) (50 mg, 0.0848 mmol) was treated with hydroxylamine. Purification by reverse phase HPLC, using acetonitrile:water:TFA as eluant, provided the title hydroxamic acid (22 mg, 32%) as bis-TFA salt. MS found: (M+H) *=577.

Example 210

2-[(3S,4S)-4-[(hydroxyamino)carbonyl]-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)piperidinyl]-2-methylpropanoic acid bis(trifluoroacetate)

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(210a) Following a procedure similar to that used for reaction (109a), the hydroxamic acid from reaction (209b) was treated with TFA. Purification by reverse phase HPLC, using acetonitrile:water:TFA as eluant, provided the title hydroxamic acid (8 mg, 58%) as bis-TFA salt. MS found: (M+H) +521.

Example 211

methyl 2-[(3S,4S)-4-[(hydroxyamino)carbonyl]-3-({4-[(2-15 methyl-4-quinolinyl)methoxy]benzoyl}amino)piperidinyl]-2methylpropanoate bis(trifluoroacetate)

(211a) Following a procedure similar to that used for reaction (209a), The amine from reaction (138a) (200 mg, 0.296 mmol) was treated with methyl 2-bromoisobutyrate (0.55 mL, 10 eq). Purification of the residue by silica gel column chromatography (5:95, methanol:methylene chloride) gave the desired tertiary amine (150 mg, 93%). MS found: (M+H) +=548.

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(211b) Following a procedure similar to that used for reaction (100b), the tertiary amine from reaction (211a) (150 mg, 0.274 mmol) was treated with hydroxylamine. Purification by reverse phase HPLC, using acetonitrile:water:TFA as eluant, provided the title hydroxamic acid (40 mg, 20%) as bis-TFA salt. MS found: (M+H) +=535.

Example 212

(3S, 4S) -N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-[2-(4-morpholinyl)-2-oxoethyl]-4-piperidinecarboxamide bis(trifluoroacetate)

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(212a) Following a procedure similar to that used for reaction (209a), The amine from reaction (138a) (2.00 g, 2.96 mmol) was treated with tert-butyl bromoacetate (1.15 g, 2 eq). Purification of the residue by silica gel column chromatography (ethyl acetate) gave the desired tertiary amine (1.40 g, 80%). MS found: (M+H)⁺=562.

(212b) Following a procedure similar to that used for reaction (109a), the tertiary amine from reaction (212a)
(1.20 g, 2.14 mmol) was treated with TFA. The mixture was concentrated in vacuo to provide the desired carboxylic acid (1.70 g, 100%) as bis-TFA salt. MS found: (M+H) +=506.

(212c) Following a procedure similar to that used for reaction (16f), the carboxylic acid from reaction (212b) (300 mg, 0.378 mmol) was treated with morpholine. Purification of the residue by silica gel column chromatography (5:95, methanol:methylene chloride) gave the desired amide (130 mg, 60%). MS found: (M+H) +=575.

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(212d) Following a procedure similar to that used for reaction (100b), the amide from reaction (212c) (130 mg, 0.226 mmol) was treated with hydroxylamine. Purification by reverse phase HPLC, using acetonitrile:water:TFA as eluant, provided the title hydroxamic acid (70 mg, 40%) as bis-TFA salt. MS found: (M+H)⁺=562.

Example 213

(3S, 4S) -1-[2-(dimethylamino)-2-oxoethyl]-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4piperidinecarboxamide bis(trifluoroacetate)

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(213a) Following a procedure similar to that used for reaction (16f), the carboxylic acid from reaction (212b) (300 mg, 0.378 mmol) was treated with dimethylamine hydrogen chloride. The crude amide (200 mg) was used for the next step without further purification. MS found: (M+H)⁺=533.

(213b) Following a procedure similar to that used for reaction (100b), the amide from reaction (213a) (200 mg, 0.378 mmol) was treated with hydroxylamine. Purification by reverse phase HPLC, using acetonitrile:water:TFA as eluant, provided the title hydroxamic acid (90 mg, 32% for two steps) as bis-TFA salt. MS found: (M+H) *=520.

Example 214

20 (3S,4S)-1-(1,1-dimethyl-2-propenyl)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4-piperidinecarboxamide bis(trifluoroacetate)

(214a) A mixture of the intermediate from (186a) (1.0 g, 1.95 mmol) and Pd/BaSO₄ (0.10g, 5% wt.) in ethanol (50 mL) was stirred under a hydrogen balloon for 40 min. After removal of catalyst by filtration, the filtrate was concentrated and purified by silica gel chromatography (5% methanol/dichloromethane) to yield the alkene (0.87 g, 87%). 30 MS found: (M+H) +=516.

(214b) Following a procedure analogous to that used in reaction (1d), the ethyl ester (0.15 g, 0.29 mmol) from reaction (214a) was treated with hydroxylamine solution.

Purification by reverse phase HPLC (15-40% acetonitrile/water) yielded the desired hydroxamic acid (0.09 g, 43%). MS found: (M+H)+=503.

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Example 215

(3S, 4S) -N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-tert-pentyl-4-piperidinecarboxamide bis(trifluoroacetate)

10 (215a) A mixture of the intermediate from (214a) (0.20 g, 0.388 mmol) and Rh/C (20 mg, 5% wt.) in ethanol (20 mL) was stirred under a hydrogen balloon for 4 h. After removal of catalyst by filtration, the filtrate was purified by silica gel chromatography (5% methanol/dichloromethane) to yield the alkane (0.176 g, 88%). MS found: (M+H) +=518.

(215b) Following a procedure analogous to that used in reaction (1d), the ethyl ester (0.12 g, 0.23 mmol) from reaction (215a) was treated with hydroxylamine solution. Purification by reverse phase HPLC (15-40% acetonitrile/water) yielded the desired hydroxamic acid (82)

mg, 48%). MS found: (M+H) +=505.

Example 216

25 (3*S*, 4*S*) -*N*-hydroxy-3-({4-[(2-methyl-4-

quinolinyl)methoxy]benzoyl}amino)-1-(2-propynyl)-4piperidinecarboxamide bis(trifluoroacetate)

(216a) A mixture of the free base of the intermediate from (138a) (0,30 g, 0.67 mmol), propargyl bromide (80% wt. in toluene, 0.1 mL, 0.90 mmol), potassium carbonate (0.46 g, 5 eq) and sodium iodide (0.135 g, 1.35 eq) in acetone (10 mL) was refluxed for 2 h. The mixture was then cooled to room temperature, quenched with saturated NH₄Cl (20 mL), extracted

with ethyl acetate (2 x 20 mL), washed with brine (10 mL), dried (MgSO₄) and concentrated. Silica gel chromatography (5% methanol/dichloromethane) yielded the desired product- (0.27 g, 83%). MS found: $(M+H)^+=486$.

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(216b) Following a procedure analogous to that used in reaction (1d), the ethyl ester (0.25 g, 0.52 mmol) from reaction (216a) was treated with hydroxylamine solution. Purification by reverse phase HPLC (15-40%

acetonitrile/water) yielded the desired hydroxamic acid (0.26 g, 72%). MS found: (M+H) +473.

Example 217

(3S,4S)-1-allyl-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4-piperidinecarboxamide bis(trifluoroacetate)

(217a-b) Following procedures analogous to that used in reaction (186a) and (1d), the intermediate from reaction (138a) (0.20 g, 0.45 mmol) was alkylated with allyl bromide, then treated with hydroxylamine solution. Purification by reverse phase HPLC (15-40% acetonitrile/water) yielded the desired hydroxamic acid (75 mg, 26% for 2 steps). MS found: (M+H) +=475.

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Example 218

(3S, 4S) -N-hydroxy-1-(1-methyl-2-propynyl)-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4-piperidinecarboxamide bis(trifluoroacetate)

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(218a-b) Following procedures analogous to that used in reaction (186a) and (1d), the intermediate from reaction (138a) (0.20 g, 0.45 mmol) was alkylated with 3-chloro-1-butyne, then treated with hydroxylamine solution.

Purification by reverse phase HPLC (15-40% acetonitrile/water) yielded the desired hydroxamic acid (100.5 mg, 40% for 2 steps). MS found: $(M+H)^+=487$.

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Example 219

(3S, 4S) -N-hydroxy-1-(1-methyl-2-propenyl)-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4-piperidinecarboxamide bis(trifluoroacetate)

10 (219a) A mixture of hydroxamic acid from example 218 (20 mg, 0.028 mmol) and 5% wt. Pd/BaSO4 (4 mg, 20% wt.) in methanol (2 mL) was stirred under a hydrogen-balloon for 20 min. After removal of catalyst by filtration, the filtrate was concentrated and lyophilized to yield the title product (17 mg, 87%). MS found: (M+H) +=489.

Example 220

 $N-\{(1R,2S)-4,5-dihydroxy-2-$

[(hydroxyamino)carbonyl]cyclohexyl}-4-[(2-methyl-4-quinolinyl)methoxy]benzamide trifluoroacetate

(220a) To a -20°C solution of 1-methyl-(1S, 2R)-(+)-cis-1,2,3,6-tetrahydrophthalate (2.21 g, 12.0 mmol) and triethylamine (3.34 mL, 2.0 eq) in tetrahydrofuran (30 mL) was added ethyl chloroformate (1.72 mL, 1.5 eq). After 5 min at -20°C, the CCl₄/dry ice bath was replaced with ice-water bath. A solution of sodium azide (1.95 g, 2.5 mmol) in water (10 mL) was added. The mixture was stirred at ambient temperature for 30 min, diluted with water (50 mL), extracted with ethyl acetate (2X100 mL), washed with brine (50 mL), dried (MgSO₄), and concentrated. The oil residue was treated with benzene (30 mL) and heated to reflux for 1 h. The mixture was finally treated with 1 N hydrochloric acid (24 mL) and stirred at room temperature for 40 h. The

aqueous layer was separated, washed with ethyl ether (2x5 mL), concentrated and pumped in vacuo to yield the desired amine hydrochloride (1.40 g, 61%).

5 (220b) Following a procedure analogous to that used in reaction (16f), the amine hydrochloride (1.20 g, 5.72 mmol) from reaction (220a) was coupled with 4-(2-methyl-4-quinolinylmethoxy)benzoic acid. Silica gel chromatography (60% then 70% ethyl acetate/hexane) provided the desired amide (1.40 g, 57%). MS found: (M+H) +=431.

(220c) To a mixture of the amide from reaction (220b) (0.30 g, 0.70 mmol) in water (1 mL) and acetone (8 mL) was added 4-methylmorpholine N-oxide (0.16 g, 2 eq) and OsO₄ (4% in water, 0.2 mL, 0.05 eq). After 4 h at room temperature, the reaction was quenched with 30% NaHSO₃ (3 mL), and stirred for 30 min before extracted with ethyl acetate (2X50 mL). The extracts were combined, washed with water (10 mL), brine (10 mL), dried (MgSO₄), and concentrated. Purification by silica gel chromatography (5% methanol/dichloromethane) and recrystallization from methanol yielded the lower Rf isomer as the desired diol (0.16 g, 50%). MS found: (M+H)+=465.

(220d) Following a procedure analogous to that used in reaction (1d), the diol from reaction (220c) (0.15 g, 0.30 mmol) was treated with hydroxylamine solution. Purification by reverse phase HPLC (15-40% acetonitrile/water) yielded the desired hydroxamic acid (98 mg, 55%). MS found: (M+H)*=466.

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Example 221

(5S)-N-hydroxy-5-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-2-oxo-4-piperidinecarboxamide trifluoroacetate

(221a) A solution of benzyl (S)-(-)-tetrahydro-5-oxo-3-furanyl carbamate (2.00 g, 8.50 mmol) in THF (50 mL) was added dropwise to LDA (17.9 mmol, 2.1 eq) in THF (150 mL) at -78°C over 10 minutes. After additional 10 min at that temperature, tert-butyl bromoacetate (3.77 mL, 3 eq) was added. The mixture was stirred at -78°C for 1 h, quenched with a solution of acetic acid (1 mL) in THF (4 mL) and warmed to rt. Following removal of solvent in vacuo, the residue was diluted with ethyl acetate (300 mL), washed with water (2x10 mL), and brine (10 mL), dried (MgSO₄) and concentrated. - 1H-NMR analysis of the crude material indicated presence of two isomers in 3:2 ratio. Silica gel column chromatography (2:8, ethyl acetate:hexanes) gave the major lactone (950 mg, 32%). MS found: (M+Na)*=506.

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(221b) The lactone from reaction (221a) (2.70 g, 7.72 mmol) in THF (40 mL) was treated with 1 N LiOH (10 mL, 1.3 eq) at 0 °C and stirred at that temperature for 1 h. The mixture was adjusted to pH4-5 with 1 N HCl and concentrated. The residue was diluted with ethyl acetate (200 mL), washed with water (10 mL), brine (10 mL), dried (MgSO₄) and concentrate in vacuo. The crude carboxylic acid (3.00 g) was taken to the next step without further purification. MS found: (M+Na)+390.

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(221c) The crude carboxylic acid from reaction (221b) (3.00 g) in methanol (20 mL) and benzene (80 mL) was treated with 2.0 M hexane solution of (trimethylsilyl)diazomethane (5 mL, 1.3 eq) at rt. After 10 min at rt, the mixture was concentrated and purified by silica gel column chromatography (3:7, ethyl acetate:hexanes) to provide the desired methyl ester (1.46 g, 50% for two steps). MS found: (M+Na)*=404.

(221d) The ester from reaction (221c) (780 mg, 2.04 mmol) in methylene chloride (20 mL) was treated with triethylamine (0.43 mL, 1.5 eq) and methanesulfonyl chloride (0.19 mL, 1.3 eq) at 0°C and stirred at that temperature for 1 h. The mixture was quenched with saturated NaHCO₃ (10 mL) and diluted with ethyl acetate (200 mL). The mixture was washed with water (10 mL), and brine (10 mL), dried (MgSO₄) and concentrated. The residue was purified by silica gel column chromatography (3:7, ethyl acetate:hexanes) to provide the desired mesylate (870 mg, 93%). MS found: (M+H)*=460.

(221e) The mesylate from reaction (221d) (700 mg, 1.52 mmol) and sodium azide (990 mg, 10 eq) were dissolved in DMF (10 mL) and heated to 90°C for 1 h. The mixture was cooled down to rt, treated with saturated NaHCO₃ (5 mL) and ethyl acetate (200 mL), washed with water (10 mL), brine (10 mL), dried (MgSO₄) and concentrate in vacuo. Purification of the residue by silica gel column chromatography (2:8, ethyl acetate:hexanes) gave the desired azide (580 mg, 94%). 1H

NMR showed a 4:1 mixture due to partial epimerization at alpha position of the ester. MS found: (M+H)+=407.

(221f) The azide from reaction (221e) (190 mg, 0.467 mmol) in methanol (4 mL) was treated with tin(II) chloride (177 mg, 2 eq) and stirred at rt for 2 h. Additional portion of tin(II) chloride (177 mg, 2 eq) was added and the mixture stirred for 2 h. Following addition of saturated NaHCO₃ (5 mL) and ethyl acetate (100 mL), the mixture was washed with water (2x5 mL), and brine (5 mL), dried (MgSO₄), treated with 1 N HCl in ether (1 mL) and concentrated. The crude amine hydrochloride salt (220 mg) was taken to the next step without further purification. MS found: (M+H)⁺=381.

(221g) Following a procedure similar to that used for reaction (109a), the amine from reaction (221f) (220 mg) was

treated with TFA. The crude carboxylic acid (250 mg) was taken to the next step without further purification. MS found: $(M+H)^+=325$.

- 5 (221h) Following a procedure similar to that used for reaction (16f), the carboxylic acid from reaction (212g) (280 mg) was treated with BOP reagent. Purification of the residue by silica gel column chromatography (7:3 ethyl acetate:hexane, then 5:95 methanol:methylene chloride) gave the desired lactam (29 mg, 20% for 3 steps). MS found: (M+Na)+329.
- (221i) The lactam from reaction (221h) 7(29 mg, 0.0948 mmol) in methanol (8 mL) was treated with 20% Pd(OH)₂ on carbon (20 mg) and stirred under hydrogen balloon for 2 h. The mixture was filtered and the filtrate was concentrated to provide the desired amine (16 mg, 100%). MS found: (M+CH₃CN)+=205.
- (221j) Following a procedure similar to that used for
 reaction (16f), the amine from reaction (212i) (15 mg,
 0.0871 mmol) was coupled with 4-(2-methyl-4quinolinylmethoxy)benzoic acid. Purification of the residue
 by silica gel column chromatography (7:3 ethyl
 acetate:hexanes, then 5:95 methanol:methylene chloride) gave
 the amide compound (25 mg, 64%). MS found: (M+H) +=448.
 - (221k) Following a procedure similar to that used for reaction (100b), the intermediate from reaction (221j) (25 mg, 0.0559 mmol) was treated with hydroxylamine.
- Purification by reverse phase HPLC, using acetonitrile:water:TFA as eluant, provided the title hydroxamic acid (6.5 mg, 21%) as bis-TFA salt. MS found: (M+H) +=449.

Example 222

(3S, 4S) -N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-2-oxo-4-piperidinecarboxamide trifluoroacetate

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(222a) Isobutylene (100 mL) was condensed into a solution of L-ASP(OMe)-OH hydrogen chloride (10.0 g, 54.4 mmol) in dioxane (100 mL) and sulfuric acid (10 mL) in a 350-mL pressure bottle. The resultant mixture was shaken mechanically at rt for 4 h and poured into a cold mixture of 1 N NaOH (500 mL) and ether (250 mL). The aqueous phase was extracted with ethyl acetate (3x200 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄) and concentrated to provide the desired ester (2.10 g, 19%). MS found: (M+H)+=204.

(222b) Following a procedure similar to that used for reaction (126a), the ester from reaction (222a) (2.10 g, 10.3 mmol) was treated with benzaldehyde (1.26 mL, 1.2 eq). Purification of the residue by silica gel column chromatography (3:7 ethyl acetate:hexanes) gave the desired amine (2.00 g, 66%). MS found: (M+H) += 294.

(222c) A mixture of the amine for reaction (222b) (2.60 g, 8.86 mmol), potassium phosphate (3.76 g, 2 eq), Lead (II) nitrate (2.35 g, 0.8 eq) and 9-phenylfluorenyl-9-bromide (3.13 g, 1.1 eq) in acetonitrile (100 mL) was shaken at rt for 15 h. Following addition of methylene chloride (200 mL and the mixture was filtered through a silica gel pad. The filtrate was concentrated and purified by silica gel column chromatography (1:9 ethyl acetate:hexanes) to provide the desired tertiary amine (4.80 g, 100%). MS found: (M+Na) +556.

(222d) A 0.5 M toluene solution of potassium

bis(trimethylsilyl)amide (32.2 mL, 2 eq) and allyl iodide

(1.47 mL, 2 eq) were added sequentially to a solution of the
amine from reaction (222c) (4.30 g, 8.06 mmol) in THF (100

5 mL) at -20°C. After 2 h at -20°C, the mixture was quenched
with pH7 phosphate buffer (30 mL). The aqueous phase was
extracted with ethyl acetate (2x100 mL). The combined
organic layers were washed with brine (20 mL), dried (MgSO₄)
and concentrated. ¹H NMR analysis of the crude material

10 showed a 5:1 mixture of two isomers. Silica gel column
chromatography (5:95 ethyl acetate:hexanes) gave the major
isomer (3.00 g, 78%). MS found: (M+Na)*=596.

(222e) O₃ was bubbled into a solution of the intermediate

from reaction (222d) (500 mg, 0.872 mmol) in methylene
chloride (30 mL) at -78°C until the solution turned blue
(approximately 2 min). The mixture was bubbled with N₂ until
the blue color disappeared, and then treated with
triphenylphosphine (458 mg, 2 eq). After 4 h at rt, the

mixture was concentrated and purified by silica gel column
chromatography (1:9 ethyl acetate:hexanes) to provide the
desired aldehyde (380 mg, 76%). MS found: (M+Na) +=598.

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(222f) Sodium triacetoxyborohydride (423 mg, 6 eq) was added to a solution of the aldehyde from reaction (222e) (190 mg, 0.330 mmol) and ammonium acetate (255 mg, 10 eq) in acetic acid (2 mL) and acetonitrile (2 mL) at 0°C. After 30 minutes at 0°C, another portion of sodium triacetoxyborohydride (282 mg, 4 eq) was added. After an additional 30 minutes at 0°C, the mixture was diluted with ethyl acetate (100 mL) and washed with saturated ammonium chloride (5 mL), brine (5 mL), dried (MgSO₄) and concentrated. Purification of the residue by silica gel column chromatography (1:1 ethyl acetate:hexanes, then 1:9 methanol:methylene chloride) gave

the desired primary amine (80 mg, 42%). MS found: $(M+H)^+=577$.

(222g) The amine from reaction (222f) (80 mg, 0.139 mmol) was treated with TFA (2 mL) at rt for 3 h and concentrated. The crude carboxylic acid (70 mg) was taken to the next step without further purification. MS found: (M+H) +=281.

(222h) Following a procedure similar to that used for
reaction (16f), the carboxylic acid from reaction (222g) (70 mg) was treated with BOP reagent. Purification of the residue by silica gel column chromatography (1:1 ethyl acetate:hexane, then 5:95 methanol:methylene chloride) gave the desired lactam (25 mg, 69% for 2 steps). MS found:
15 (M+H) +263.

(222i-k) Following the procedure similar to that used for steps from (221i-k), but using the lactam from reaction (222h) (25 mg, 0.0953 mmol), the title compound was prepared. The product was purified by reverse phase HPLC, using acetonitrile:water:TFA as eluant, to provide the desired hydroxamic acid (6.5 mg, 13% for 3 steps) as bis-TFA salt. MS found: (M+H) +=449.

25 **Example 223**

(3S, 4S) -3-{[4-(2-butynyloxy)benzoyl]amino}-N-hydroxy-1-isopropyl-4-piperidinecarboxamide trifluoroacetate

(223a) The intermediate from reaction (134e) (1.0 g, 1.83 30 mmol) was treated with Pd(OH)₂/C (0.20 g, 20% wt.) and ethanol (20 mL). The resulting mixture stirred under hydrogen balloon overnight. After removal of catalyst by filtration, the filtrate was concentrated and purified by silica gel chromatography to yield the phenol (0.60 g, 84%). 35 MS found: (M+H)+=393.

(223b) The phenol from reaction (223a) (0.10 g, 0.26 mmol) was alkylated with 1-bromo-2-butyne (0.03 mL, 1.3 eq) and K₂CO₃ (0.18 g, 5 eq) in acetonitrile (5 mL) at reflux for 3 h. The mixture was cooled to room temperature and partitioned between water (10 mL) and ethyl acetate (50 mL). The organic layer was separated, dried (MgSO₄), concentrated and purified by silica gel chromatography (40% ethyl acetate/hexane) to yield the desired product (0.11 g, 99%).
10 MS found: (M+H)⁺=445.

(223c) The intermediate from reaction (223b) (0.10 g, 0.23 mmol) was treated with dichloromethane (2 mL) and trifluoroacetic acid (1 mL) at room temperature for 1 h, then concentrated and pumped in vacuo overnight to give the amine TFA salt (0.1 g, 100%). MS found: (M+H) +=345.

(223d-e) Following procedures analogous to that used in reaction (16h) and (1d), the intermediate from reaction (223c) (72 mg, 0.16 mmol) was converted to the title compound (37 mg, 71%). MS found: (M+H)+=374.

Example 224

(3S, 4S) -3-{[4-(2-butynyloxy)benzoyl]amino}-N-hydroxy-4-piperidinecarboxamide trifluoroacetate

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(224a) Following a procedure analogous to that used in reaction (1d), the intermediate from reaction (223c) (27 mg, 0.08 mmol) was converted to the title compound (10 mg, 28%). 30 MS found: (M+H) +=332.

Example 225

tert-butyl (3S,4S)-4-[(hydroxyamino)carbonyl]-3-({4-[(2methyl-3-pyridinyl)methoxy]benzoyl}amino)-1piperidinecarboxylate trifluoroacetate

(225a) To a 0°C solution of the phenol from reaction (223a) (0.10 g, 0.255 mmol) and 2-methyl-3-hydroxymethyl-pyridine (38 mg, 1.2 eq) in THF (2 mL) was added triphenylphosphine (80 mg, 1.2 eq) and diethyl azodicarboxylate (0.05 mL, 1.2 eq). After stirred at room temperature overnight, the mixture was quenched with saturated NH₄Cl, extracted with ethyl acetate (2x20 mL), dried (MgSO₄), concentrated and purified by silica gel chromatography (80% ethyl acetate/hexane) to yield the desired product (0.12 g, 100%). MS found: (M-H) =496.

(225b) Following a procedure analogous to that used in reaction (1d), the intermediate from reaction (225a) (0.12 15 g, 0.25 mmol) was treated with hydroxylamine solution. Purification by reverse phase HPLC (25-50% acetonitrile/water) yielded the desired hydroxamic acid (67 mg, 52%). MS found: (M+H) *=485.

20 Example 226

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(3S,4S)-N-hydroxy-3-({4-[(2-methyl-3-pyridinyl)methoxy]benzoyl}amino)-4-piperidinecarboxamide bis(trifluoroacetate)

25 (226a) The hydroxamic acid from reaction (225b) (20 mg, 0.033 mmol) was treated with dichloromethane (2 mL) and trifluoroacetic acid (0.2 mL) at room temperature for 1 h. After removal of solvent in vacuo, the residue was purified by reverse phase HPLC (5-30% acetonitrile/water) to yield 30 the titled compound (10 mg, 49%). (M+H)+=385.

Example 227

tert-butyl (3S,4S)-3-({4-[(2,5dimethylbenzyl)oxy]benzoyl}amino)-4[(hydroxyamino)carbonyl]-1-piperidinecarboxylate

(227a) To a mixture of the phenol from reaction (223a) (0.10 g, 0.255 mmol) and 2,5-dimethylbenzyl chloride (0.05 mL, 1.3 eq) in DMSO (1 mL) was added sodium iodide (51 mg, 1.3 eq) and Cs₂CO₃ (0.25 g, 3.0 eq). After 2 h at room temperature, the reaction mixture was quenched with saturated NH₄Cl, extracted with ethyl acetate (2x20 mL), dried (MgSO₄), concentrated and purified by silica gel chromatography (50% ethyl acetate/hexane) to yield the desired product (0.10 g, 7.7%)... MS found: (M+H) =541.

(227b) Following a procedure analogous to that used in reaction (1d), the intermediate from reaction (227a) (0.10 g, 0.20 mmol) was converted to the desired hydroxamic acid (92 mg, 97%). MS found: (M-H) = 496.

Example 228

(3S, 4S) -3- $(\{4-[(2, 5-dimethylbenzyl)oxy]benzoyl\}amino)-N-hydroxy-4-piperidinecarboxamide trifluoroacetate$

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(228a) The hydroxamic acid from reaction (227b) (26 mg, 0.053 mmol) was treated with dichloromethane (2 mL) and trifluoroacetic acid (1 mL) at room temperature for 1 h. After removal of solvent in vacuo, the residue was purified by reverse phase HPLC (30-55% acetonitrile/water) to yield the titled compound (9.5 mg, 35%). (M+H) +=398.

Example 301

(cis,cis)-3-Amino-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-(Nhydroxy)cyclohexylcarboxamide bis-trifluoroacetate salt

(301a) To a solution of 3-hydroxy-2-nitrobenzoic acid (10 g, 54.6 mmol) in EtOH (150 mL) and benzene (150 mL) was added concentrated sulfuric acid (40 mL). The mixture was heated

at reflux for 48 hours with azeotropic removal of water and concentrated on a rotary evaporator. The residue was dissolved in EtOAc (200 mL) and the resulting solution was washed with saturated NaHCO3 (2x100 mL) and brine (2x100 mL). The organic layer was dried (MgSO₄) and concentrated on a rotary evaporator to give the ethyl ester (11g, 95%) as a solid. MS-ESI $(M+H)^+=212.1$.

- (301b) The above compound (11g, 52.1 mmol) was mixed with 10 0.5% aqueous HCl (200 mL) and PtO_2 (2.2 g) in a Parr bottle. The mixture was hydrogenated on a Parr shaker at 55 psi for 24 hours. The catalyst was filtered off and the filtrate was concentrated on a rotary evaporator. The residue was dried in vacuo to give the crude ethyl 2-amino-3-
- 15 hydroxycyclohexylcarboxylate (12 g, 100%). MS-ESI $(M+H)^{+}=188.1$
- (301c) To a solution of 301b (1.8 g, 8 mmol) and 4-[(2methyl-4-quinolinyl)methoxylbenzoic acid (1.7 g, 6 mmol) in 20 DMF (10 mL) cooled in an ice bath was added BOP (3.1 q, 7 mmol) followed by N-methylmorpholine (3 g, 30 mmol). The mixture was stirred at room temperature overnight. EtOAc (100 mL) was added and the solution was washed with brine (2x50 mL), NaHCO₃ (2x50 mL) and brine (2x50 mL), dried $(MgSO_4)$ and concentrated on a rotary evaporator. The crude 25 product was chromatographed on a silica gel column (10% $MeOH/CH_2Cl_2$) to provide 301c (0.8 g, 30%) as a solid. MS-ESI $(M+H)^{+}=449.2.$
- 30 (301d) Compound 301c (350 mg, 0.78 mmol) was dissolved in chloroform (10 mL)/TFA (0.5 mL). To it was added Dess-Martin periodinane (365 mg, 0.86 mmol) and the solution was stirred for 2 hours. Insoluble material was filtered off and the filtrate was concentrated on a rotary evaporator to provide the crude ketone product as a solid. MS-ESI (M+H) +=461.2.
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(301e) To a solution of 301d (120 mg, 0.21 mmol) in DMF (2 mL) was added acetic acid (0.2 mL) followed by NH₄OAc (90 mg, 1.2 mmol) and Na(OAc)₃BH (120 mg, 0.6 mmol). The mixture was stirred at room temperature for 3 hours and purified using reverse phase HPLC to provide the amino product (55 mg, 40%) as a powder. MS-ESI (M+H)⁺=462.3.

(301f) Compound 301e (40 mg, 0.058 mmol) was dissolved in

DMF (1 mL) and to it was added N-methylmorpholine (40 mg, 0.4 mmol) followed by di-tert-butyl-dicarbonate (22 mg, 0.1 mmol). The mixture was stirred at room temperature for 5 hours and purified using reverse phase HPLC to provide the Boc-protected product (20 mg, 51%) as a powder. MS-ESI

(M+H) *=562.3.

(301g) A mixture of 301f (20 mg, 0.03 mmol) in MeOH (2 mL) and 1 N KOH (0.5 mL) was heated at 60 °C for 1 hour and the solution was concentrated on a rotary evaporator. The residue was dissolved in DMSO/HOAc and purified using reversed phase HPLC to provide the carboxylic acid (16 mg, 83%) as a powder. MS-ESI (M+H) *=534.2.

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(301h) To a solution of 301g (15 mg, 0.023 mmol) in DMF (1 mL) was added N-methylmorpholine (20 mg, 0.2 mmol) followed by hydroxylamine hydrochloride (10 mg, 0.14 mmol). After all solid was dissolved, the solution was cooled in an ice bath and to it was added BOP (22 mg, 0.05 mmol). The mixture was stirred for 30 min at room temperature. Purification using reversed phase HPLC provided the hydroxamic acid (10 mg, 67%) as a powder. MS-ESI (M+H) *=549.3.

(301i) Compound 301h (10 mg) was dissolved in a mixed solvent of 40% TFA in CH_2Cl_2 (1 mL) and after 30 min, the solvent was removed by evaporation. The residue was

dissolved in water/acetonitrile. Lyophilization provided the desired product as a powder. MS-ESI (M+H) +=449.3.

Example 302

(cis, cis) -3-Methylamino-2-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-(N-hydroxy)cyclohexylcarboxamide bis-trifluoroacetate salt

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(302a) To a solution of 301d (100 mg, 0.17 mmol) in DMF (1 mL) was added HOAc (48 mg, 0.8 mmol) followed by methylamine (2 M solution in THF, 0.4 mL, 0.8 mmol) and Na(OAc)₃BH (80 mg, 0.4 mmol). The mixture was stirred for 3 hours at room temperature. Purification using reversed phase HPLC provided the methylamino product (70 mg, 58%) as a powder. MS-ESI (M+H)⁺=476.3.

(302b) Compound 302a (70 mg, 0.1 mmol) was reacted with ditert-butyl-dicarbonate using the procedure described in (301f) to provide the Boc-protected product (55 mg, 80%) as a powder. MS-ESI (M+H)⁺=576.3.

(302c) The final product was obtained by saponification of the ethyl ester 302b followed by coupling of the carboxylic acid with hydroxylamine hydrochloride and removal of the Boc group using procedures similar to those described in (301g)-(301i). MS-ESI (M+H)+=463.3.

Example 303

(cis, cis) -3-Dimethylmino-2-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(N-hydroxy)cyclohexylcarboxamide bis-trifluoroacetate salt

(303a) To a solution of 302a (100 mg, 0.14 mmol) in DMF (1 mL) was added formaldehyde (37% aqueous solution, 82 mg, 1 mmol) followed by N-methylmorpholine (100 mg, 1 mmol) and

Na(OAc)₃BH (84 mg, 0.4 mmol). The mixture was stirred for 2 hours at room temperature. Purification using reversed phase HPLC provided the dimethylamino product (100 mg, 99%) as a powder. MS-ESI $(M+H)^+=490.2$.

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(303b) The final compound was obtained by saponification of the ethyl ester 303a followed by coupling the resulting carboxylic acid with hydroxylamine hydrochloride using procedures similar to those described in (301g) and (301h).

10 MS-ESI (M+H)*=477.3.

Example 304

(cis, trans)-3-Amino-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(Nhydroxy)cyclohexylcarboxamide bis-trifluoroacetate salt

(304a) To a solution of 301b (3.6 g, 16 mmol) and 4-benzyloxybenzoic acid (3.7 g, 16 mmol) in DMF (10 mL) cooled in an ice bath was added BOP (8 g, 18 mmol) followed by N-methylmorpholine (7.4 mL, 64 mmol). The mixture was stirred at room temperature overnight and diluted with EtOAc (150 mL). The resulting solution was washed with NaHCO₃ (2x70 mL) and brine (2x70 mL), dried (MgSO₄) and concentrated on a rotary evaporator. The residue was chromatographed on a silica gel column (5% MeOH/CH₂Cl₂) to provide the amide product (2.3 g, 36%) as a solid. MS-ESI (M+H) +=398.2.

(304b) To a solution of 304a (2.3 g, 5.8 mmol) in CHCl₃ (15 mL) cooled in an ice bath was added N-methylmorpholine (1.1 mL, 10 mmol) followed by methanesulfonyl chloride (0.7 g, 6 mmol). The mixture was stirred in the ice bath for 2 hours and at room temperature overnight. The solvent was removed by concentration and the residue was dissolved in EtOAc. The resulting solution was washed with brine, dried (MgSO₄) and concentrated. Chromatography on a silica gel column (50%

EtOAc/hexane) provided the mesylate (1.6 g, 60%) as a solid. $MS-ESI (M+H)^{+}=476.2.$

(304c) A mixture of 304b (1.2 g, 2.5 mmol) and sodium azide (0.33 g, 5.1 mmol) in DMF (15 mL) was heated at $100 \, ^{\circ}\text{C}$ for 5 hours. DMF was removed by evaporation in vacuo. The residue was dissolved in EtOAc and the resulting solution was washed with brine, dried (MgSO₄) and concentrated. Chromatography on a silica gel column (40% EtOAc/hexane) provided the azido product (0.69 g, 65%) as a solid. MS-ESI (M+H)+=423.1. 10

(304d) Compound 304c (0.69 g, 1.6 mmol) was dissolved in MeOH (20 mL) in a Parr bottle and to it was added 4 N HCl in dioxane (0.5 mL) followed by 10% Pd-C (0.1 g). The mixture was hydrogenated on a Parr shaker at 50 psi for 4 hours. The 15 catalyst was filtered off and the filtrate was concentrated on a rotary evaporator to provide the amino product (0.55 g, 99%) as a solid. $MS=ESI_{--}(M+H)^{+}=307.2$.

- (304e) To a solution of 304d (0.55 g, 1.6 mmol) in THF (15 20 mL) and water (2 mL) cooled in an ice bath was added 1 N NaOH (1.6 mL) followed by NaHCO3 (0.5 g, 6 mmol) and di-tertbutyl-dicarbonate (0:35 g, 1.6 mmol). The mixture was stirred 4 hours at room temperature. EtOAc (150 mL) was 25 added and the solution was washed with brine (2x60 mL), dried (MgSO₄) and concentrated on a rotary evaporator to give the crude Boc-protected product that was used for the next reaction without purification. MS-ESI (M+H) +=407.2.
- (304f) A mixture of 304e (0.65 g, 1.6 mmol), 4-chloromethyl-30 2-methylquinoline (0.36 g, 1.6 mmol) and K₂CO₃ (1 g, 7.2 mmol) in acetone (15 mL) was heated at reflux for 4 hours. EtOAc (150 mL) was added and the resulting solution was washed with brine (2x60 mL), dried (MgSO₄), and concentrated 35 on a rotary evaporator. Purification using reversed phase

HPLC provided 304f (0.68 g, 67%) as a powder. MS-ESI $(M+H)^+=562.3$.

(304g) Compound 304f (0.37 g, 0.65 mmol) was dissolved in MeOH (5 mL) and KOH (0.15 g) in water (1 mL) was added. The mixture was heated at 50°C for 1 hour and acidified with 0.2 mL HOAc. Purification on reversed phase HPLC provided the carboxylic acid (0.25 g, 70%) as a powder. MS-ESI (M+H) +=534.2.

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- (304h) To a solution of 304g (58 mg, 0.1 mmol) in DMF (2 mL) was added hydroxylamine hydrochloride (32 mg, 0.4 mmol) followed by N-methylmorpholine (0.06 mL, 0.5 mmol). After all solid was dissolved, the solution was cooled in an ice bath. To it was added BOP (54 mg, 0.12 mmol) and the mixture was stirred for 1 hour. Purification on reversed phase HPLC provided the hydroxamic acid as a powder. MS-ESI (M+H)+549.2.
- 20 (304i) Compound 304h (30 mg) was treated with TFA (1 mL)/CH₂Cl₂ (3 mL) for 20 min and the solution was concentrated on a rotary evaporator. The residue was taken up in water/acetonitrile. Lyophilization provided the final product as a powder. MS-ESI (M+H) +=449.2.

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Example 305

(cis, trans) -3-Dimethylmino-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-(Nhydroxy)cyclohexylcarboxamide bis-trifluoroacetate salt

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(305a) Compound 304g (160 mg) was treated with TFA (1 mL)/ CH_2Cl_2 (3 mL) for 20 min and the solution was concentrated on a rotary evaporator. MS-ESI (M+H)⁺=434.2.

(305b) To a solution of 305a (50 mg, 0.075 mmol) in THF (2 mL) was added formaldehyde (37% aqueous solution, 0.04 mL, 0.42 mmol) followed by N-methylmorpholine (40 mg, 0.4 mmol) and NaBH₃CN (24 mg, 0.4 mmol). After stirring at room temperature for 1 hour, the mixture was purified on reversed phase HPLC to provide the dimethylamino product (48 mg, 92%) as a powder. MS-ESI (M+H)*=462.2.

(305c) Coupling of 305b with hydroxylamine hydrochloride using a procedure similar to that described in (304h) provided the hydroxamic acid as a powder. MS-ESI (M+H) +=477.3.

Example 306

15 (cis, trans)-3-(1-Methyl-1-ethylmino)-2-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-(N-hydroxy)cyclohexylcarboxamide bis-trifluoroacetate salt

(306a) To a solution of compound 305a (52 mg, 0.08 mmol) in THF (2 mL) was added acetone (0.1 mL) followed by N-methylmorpholine (40 mg, 0.4 mmol) and Na(OAc)₃BH (25 mg, 0.12 mmol). The mixture was stirred at room temperature overnight. Concentration on a rotary evaporator followed by purification on reversed phase HPLC provided the desired product (45 mg, 80%) as a powder. MS-ESI (M+H)⁺=476.2.

(306b) Coupling of 306a with hydroxylamine hydrochloride using a procedure similar to that described in (304h) provided the hydroxamic acid as a powder. MS-ESI (M+H) +=491.3.

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Example 307

(cis, trans)-3-Methylamino-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-(Nhydroxy)cyclohexylcarboxamide bis-trifluoroacetate salt

(307a) To a solution of compound 304d (0.166 g, 0.39 mmol) and benzaldehyde (0.042 g, 0.4 mmol) in THF (5 mL) was added Na(OAc)₃BH (0.1 g, 0.5 mmol). The mixture was stirred for 1 hour at room temperature. The product formed was a bisbenzylated product. More benzaldehyde (0.042 g, 0.4 mmol) and Na(OAc)₃BH were added. The mixture was stirred for another hour and purified on reversed phase HPLC to provide the bis-benzylated product (0.15 g, 78%) as a powder. MSESI (M+H) *=487.3.

(307b) Compound 307a (0.15 g, 0.3 mmol) was dissolved in MeOH (10 mL) and 10% Pd-C (30 mg) was added. The mixture was hydrogenated at atmospheric pressure for 3 hours. The catalyst was filtered off and the filtrate was concentrated on a rotary evaporator. Purification on reversed phase HPLC provided the mono-benzylated product (114 mg, 75%) as a powder. MS-ESI (M+H) +397.2.

- (307c) To a solution of 307b (81 mg, 0.16 mmol) and Na(OAc)₃BH (20 g, 0.32 mmol) in THF (2 mL) was added N-methylmorpholine (40 mg, 0.4 mmol) followed by formaldehyde (37% aqueous solution, 25 mg, 0.3 mmol). The mixture was stirred for 1 hour and concentrated on a rotary evaporator.
 Chromatography on a silica gel column (10% MeOH/CH₂Cl₂) provided the N-benzyl-N-methyl product (60 mg, 94%) as a solid. MS-ESI (M+H)*=411.2.
- (307d) Compound 307c (60 mg, 0.15 mmol) was dissolved in

 EtOH (5 mL) in a Parr bottle and to it was added 4 N HCl in dioxane (0.1 mL) followed by 10% Pd-C (10 mg). The mixture was hydrogenated on a Parr shaker at 50 psi for 4 hours. The catalyst was filtered off and the filtrate was concentrated on a rotary evaporator to provide the methylamino product as a solid. MS-ESI (M+H) *=321.2.

(307e) To a solution of 307d (46 mg, 0.13 mmol) in THF (4 mL)/saturated aqueous NaHCO₃ solution (1 mL) cooled in an ice bath was added 1 N NaOH (0.13 mL) followed by di-tert-butyl-dicarbonate (28 mg, 0.13 mmol). The mixture was stirred at room temperature overnight. EtOAc (50 mL) was added and the solution was washed with brine (2x20 mL), dried (MgSO₄) and concentrated on a rotary evaporator. MS-ESI (M+H)⁺=421.1.

10 (307f) A mixture of the crude product 307e, 4-chloromethyl-2-methylquinoline (30 mg, 0.13 mmol), K₂CO₃ (138 mg, 1 mmol) and Bu₄NI (20 mg, 0.13 mmol) in DMF (2 mL) was heated at 60 °C for 5 hours. Purification using reversed phase HPLC provided the desired product (68 mg, 90%) as a powder. MS-ESI (M+H) *=576.3.

(307g) The final product was obtained by saponification of the ethyl ester 307f followed by acid deprotection of the Boc group using procedures similar to those described in (304g)-(304i). MS-ESI $(M+H)^+=463.2$.

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Example 308

(cis,cis)-3-Hydroxy-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-(Nhydroxy)cyclohexylcarboxamide trifluoroacetate salt

This compound was obtained by saponification of the ethyl ester intermediate 301c followed by coupling the resulting carboxylic acid with hydroxylamine hydrochloride using procedures similar to those described in (304g) and (304h). MS-ESI $(M+H)^+=450.2$.

Example 309

N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-{[(2-methyl-35 4-quinolinyl)methyl]amino}benzamide

(309a) A mixture of methyl 4-aminobenzoate (1.51 g, 10 mmol), 4-chloromethyl-2-methylquinoline hydrochloride (2.28 g, 10 mmol) and K_2CO_3 (3.2 g, 25 mmol) in DMF (20 mL) was stirred at 100°C overnight. EtOAc (200 mL) was added. The solution was washed with water 2x, brine 2x, dried (MgSO₄) and concentrated. Flash chromatography on silica eluting with EtOAc/hexanes (2:1) provided the desired product (600 mg, 20%). MS m/z 307.1 (M+H) $^+$.

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(309b) To a solution of 309a (400 mg, 1.3 mmol) in MeOH (5 mL) and THF (5 mL) was added 1 N KOH (5 mL). The solution was stirred at 80°C for 3 h and concentrated. The residue was taken up in 1 N HCl solution (4 mL) and the solvent was removed under reduced pressure. The resulting residue was dissolved in MeOH. Insoluble materials were filtered off and the filtrate was concentrated to give the desired carboxylic acid product that was used for the next reaction without purification. MS m/z 293.2 $(M+H)^+$.

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- (309c) To a solution of 309b (200 mg, 0.684 mmol), ethyl cis-2-aminocyclopentanecarboxylate hydrochloride ($\bar{1}08$ mg, 0.6 mmol) and triethylamine (303 mg, 3 mmol) in DMF (3 mL) cooled in an ice bath was added BOP (266 mg, 0.6 mmol). The solution was stirred at room temperature for 2 h. Purification by reversed phase HPLC provided the desired product (130 mg, 34%) as a bis-trifluoroacetate. MS m/z 418.2 (M+H) $^+$.
- 30 (309d) Compound 309c (120 mg, 0.186 mmol) was dissolved in a 1.7 M hydroxylamine solution (3 mL). The reaction was stirred at room temperature for 20 min and quenched with a solution of 4 N HCl in dioxane (0.5 mL). The solvents were removed under reduced pressure and the residue was purified

by reversed phase HPLC to give the desired product (90 mg, 75%) as a powder. MS m/z 419.1 $(M+H)^+$.

Example 310

5 N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-{methyl[(2-methyl-4-quinolinyl)methyl]amino}benzamide

(310a) This compound was prepared using procedures analogous to those described for Example 309. MS m/z 433.2 (M+H)⁺.

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 $(M+H)^{+}$.

Example 311

N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-(3-phenyl-4,5-dihydro-5-isoxazolyl)benzamide

- 15 (311a) To a stirred solution of benzaldehyde oxime (605 mg, 5 mmol) and methyl 4-vinylbenzoate (810 mg, 5 mmol) in CH₂Cl₂ (20 mL) was added a bleach solution (30 mL). The mixture was stirred at room temperature for 4 h and diluted with CH₂Cl₂. The organic phase was separated, washed with brine 2x, dried (MgSO₄) and concentrated. Chromatography on a silica gel column eluting with EtOAc/hexanes (1:2) provided the desired product (500 mg, 36%) as a solid. MS m/z 323.2
- 25 (311b) To a solution of 3a (500 mg, 1.78 mmol) in THF (10 mL) was added 1 N KOH (5 mL). The solution was stirred at room temperature overnight and acidified with 1 N HCl to pH=3. The resulting solution was extracted with EtOAc 2x. The combined organic phase was washed with brine 2x, dried (MgSO₄) and concentrated to give the desired acid (400 mg, 84%). MS⁻m/z 268.2 (M+H)⁺.
 - (311c) To a solution of 3b (133 mg, 0.5 mmol), ethyl cis-2-aminocyclopentanecarboxylate hydrochloride (116 mg, 0.6 mmol) and triethylamine (303 mg, 3 mmol) in DMF (3 mL)

cooled in an ice bath was added BOP (253 mg,-0.6 mmol). The solution was stirred at room temperature for 2 h. Purification by reversed phase HPLC provided the desired product (170 mg, 84%) as a powder. MS m/z 407.1 $(M+H)^+$.

5

(311d) Compound 3c (170 mg, 0.41 mmol) was dissolved in a 1.7 M hydroxylamine solution (3 mL). After stirring at room temperature for 20 min, a solution of TFA (0.3 mL) in CH_2Cl_2 (2 mL) was added slowly. The solvents were removed under reduced pressure and the residue was purified by reversed phase HPLC to give the desired product (90 mg, 56%) as a powder. MS m/z 394.1 (M+H) $^+$.

Example 312

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N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[3-(4-pyridinyl)-4,5-dihydro-5-isoxazolyl]benzamide

(312a) This compound was prepared using procedures analogous to those described for Example 311. MS m/z 395.1 (M+H)⁺.

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Example 313

N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[3-(3-pyridinyl)-4,5-dihydro-5-isoxazolyl]benzamide

25 (313a) This compound was prepared using procedures analogous to those described for Example 311. MS m/z 395.2 (M+H)⁺.

Example 314

N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[3-(2-30 pyridinyl)-4,5-dihydro-5-isoxazolyl]benzamide

(314a) This compound was prepared using procedures analogous to those described for Example 311. MS m/z 395.2 (M+H)⁺.

Example 315

N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[3-(4-quinolinyl)-4,5-dihydro-5-isoxazolyl]benzamide

5 (315a) This compound was prepared using procedures analogous to those described for Example 311. MS m/z 445.1 (M+H)⁺.

Example 316

4-[3-(2,6-Dimethyl-4-pyridinyl)-4,5-dihydro-5-isoxazolyl]-N(cis-2-[(hydroxyamino)carbonyl]cyclopentyl)benzamide

(316a) This compound was prepared using procedures analogous to those described for Example 311. MS m/z 423.1 (M+H)⁺.

15 Example 317

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N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-3-methoxy-4-[3-(4-pyridinyl)-4,5-dihydro-5-isoxazolyl]benzamide

(317a) This compound was prepared using procedures analogous to those described for Example 311. MS m/z 425.1 (M+H)⁺.

Example 318

3-Hydroxy-N-{cis-2-[(hydroxyamino)carbonyl]cyclopentyl}-4[3-(4-pyridinyl)-4,5-dihydro-5-isoxazolyl]benzamide

(318a) This compound was prepared using procedures analogous to those described for Example 311. MS m/z 411.1 (M+H) $^+$.

Example 319

- 30 N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[5-(2-pyridinyl)-4,5-dihydro-3-isoxazolyl]benzamide
- (319a) To a solution of methyl 4-formylbenzoate (10 g, 61 mmol) in MeOH (100 mL) was added hydroxylamine hydrochloride (7 g, 100 mmol) followed by triethylamine (13.9 mL, 100

mmol). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was taken up in EtOAc (300 mL). The solution was washed with brine 3x, dried (MgSO₄), and concentrated. Flash chromatography on silica eluting with EtOAc/hexanes (2:1) provided the desired oxime product (2.5 g, 23%) as a solid. MS m/z 180.1 (M+H)⁺.

(319b) To a solution of 11a (716 mg, 4 mmol) and 2vinylpyridine (525 mg, 5 mmol) in CH₂Cl₂ (20 mL) was added a solution of bleach (30 mL). The solution was stirred at room temperature overnight and diluted with CH₂Cl₂. The organic phase was separated, washed with brine 2x, dried (MgSO₄) and concentrated. Chromatography on a silica gel column eluting with EtOAc/hexanes (2:1) provided the desired product (800 mg, 73%) as a solid. MS m/z 283.2 (M+H)⁺.

(319c) To a solution of 11b (800 mg, 2.83 mmol) in THF (5 mL) and MeOH (3 mL) was added a solution of 1 N KOH (5 mL).
20 The solution was stirred at room temperature for 4 h and acidified with a solution of 1 N HCl (6 mL). The solvents were removed under reduced pressure. The residue was dissolved in MeOH, the insoluble materials were filtered off and the filtrate was concentrated to give the desired
25 carboxylic acid that was used for the next reaction without purification. MS m/z 269.2 (M+H)⁺.

(319d) To a solution of 11c (152 mg, 0.5 mmol), ethyl cis-2-aminocyclopentanecarboxylic acid hydrochloride (116 mg, 0.6 mmol) and triethylamine (303 mg, 3 mmol) in DMF (3 mL) cooled in an ice bath was added BOP (253 mg, 0.6 mmol). The solution was stirred at room temperature for 4 h. Purification by reversed phase HPLC provided the desired product (190 mg, 73%) as a TFA salt. MS m/z 408.1 (M+H)⁺.

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(319e) Treatment of 11d with a solution of hydroxylamine following the procedure described in (311d) provided the desired hydroxamic acid. MS m/z 395.1 (M+H)⁺.

5 Example 320

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N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[5-(4-pyridinyl)-4,5-dihydro-3-isoxazolyl]benzamide

(320a) This compound was prepared using procedures analogous to those described for Example 319. MS m/z 395.1 (M+H)⁺.

Example 501

N-{4-[(hydroxyamino)carbonyl]-3-pyrrolidinyl}-1-[(2-methyl-4-quinolinyl)methyl]-1H-indole-5-carboxamide
bis(trifluoroacetate)

(501a) Indole 5-carboxylic acid (0.5 g, 3.1 mmol) was added to a suspension of sodium hydride (0.27 g, 6.8 mmol, 60% oil dispersion) (washed with hexanes) in DMF (20 mL) cooled to 0°C. The reaction was allowed to stir for 1 h and the 4-chloromethyl-2-methyl-quinoline (0.72 g, 3.8 mmol) was added. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was neutralized with 1 N HCl and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate and concentrated to give the 1-[(2-methyl-5,8-dihydro-4-quinolinyl)methyl]-1H-indole-5-carboxylic acid (0.68 g, 69%) as a brown residue, MS (M+H)*= 317.

30 (501b) Thionyl chloride (5 mL) was added to a suspension of the 1-[(2-methyl-5,8-dihydro-4-quinolinyl)methyl]-1H-indole-5-carboxylic acid from step (501a) (0.67 g, 2.1 mmol) in methylene chloride (15 mL) and was heated to reflux for 2 h. The reaction was cooled to room temperature, concentrated in vacuo to give the 1-[(2-methyl-5,8-dihydro-4-

quinolinyl)methyl]-1H-indole-5-carbonyl chloride (0.68 g, 80%) as a yellow solid.

(501c) The 1-tert-butyl 3-methyl 4-amino-1,35 pyrrolidinedicarboxylate (0.10 g, 0.41 mmol) was combined
with the acid chloride from step (501b) (0.10 g, 0.32 mmol)
in methylene chloride (15 mL) and water saturated sodium
bicarbonate (15 mL). The reaction was stirred for 3.5 h,
partitioned between methylene chloride and water. The
10 organic layer was washed with brine, dried over magnesium
sulfate and concentrated to give a solid. This was purified
by flash chromatography on silica gel eluting hexane: ethyl
acetate (30:60, v:v) to give the 1-tert-butyl 3-methyl 4[({1-[(2-methyl-4-quinolinyl)methyl]-1H-indol-5yl}carbonyl)amino]-1,3-pyrrolidinedicarboxylate (0.120 g,
70%) as a solid, MS (M+H) *= 543.

(501d) TFA (2mL) was added to a solution of the coupled
product (0.11 g, 0.2 mmol) from step (501c) in methylene
20 chloride (3 mL) at room temperature. The reaction was
complete after stirring for 2 h and was concentrated to give
methyl 4-[({1-[(2-methyl-4-quinolinyl)methyl]-1H-indol-5yl}carbonyl)amino]-3-pyrrolidinecarboxylate (0.165 g, 100%)
as an oil, MS (M+2H)**= 222.

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(501e) Following a procedure analogous to that used in example (1d) for the conversion to the hydroxamic acid, but using the methyl ester step (501d) the title compound (0.065 g. 23%) was prepared as a white amorphous solid, MS (M+H)⁺= 444.

Example 502

N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-1-[(2-methyl-4-quinolinyl)methyl]-1H-indole-5-carboxamide trifluoroacetate

(502a) Following a procedure analogous to that used in example (501) but using the methyl 2-aminocyclopentanecarboxylate, the title compound (0.038 g. 32%) was prepared as a solid, MS (M+H) += 443.

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Example 503

N-hydroxy-3-({6-[(2-methyl-4-quinolinyl)methoxy]-1-naphthoyl}amino)-4-piperidinecarboxamidebis(trifluoroacetate)

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(503a) Following a procedure analogous to that used in example (501) but using the methyl 3-amino-4-piperidinecarboxylate and 6-hydroxy-1-naphthoic acid, the title compound (0.015 g. 39%) was prepared as a white amorphous solid, MS (M+H)+= 485.

Example 504

N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-6-[(2-methyl-4-quinolinyl)methoxy]-1-naphthamide trifluoroacetate

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(504a) Following a procedure analogous to that used in example (501) but using the methyl 2-aminocyclopentanecarboxylate and 6-hydroxy-1-naphthoic acid, the title compound (0.11 g. 57%) was prepared as a white amorphous solid, MS (M+H)+= 470.

Example 505

N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-6-[(2-methyl-4-quinolinyl)methoxy]-2-naphthamide trifluoroacetate

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(505a) Following a procedure analogous to that used in example (501) but using the methyl 2-aminocyclopentanecarboxylate and 6-hydroxy-2-naphthoic acid, the title compound (0.06 g. 23%) was prepared as a white amorphous solid, MS (M+H)⁺= 470.

Example 506

N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-6-[(2-methyl-4quinolinyl)methoxy]-1,2,3,4-tetrahydro-1isoquinolinecarboxamide bis(trifluoroacetate)

(506a) Following a procedure analogous to that used in example (501) but using the methyl 2-aminocyclopentanecarboxylate and 2-(tert-butoxycarbonyl)-6-hydroxy-1,2,3,4-tetrahydro-1-isoquinolinecarboxylic acid the title compound (0.050 g. 29%) was prepared as a white amorphous solid, MS (M+H)⁺= 475.

Example 507

15 N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-1-[(2-methyl-4-quinolinyl)methyl]-1H-benzimidazole-5-carboxamide trifluoroacetate

(507a) Following a procedure analogous to that used in example (501) but using the methyl 2-aminocyclopentanecarboxylate and 1H-benzimidazole-5-carboxylic acid the title compound (0.020 g. 5%) was prepared as a white amorphous solid, MS (M+H) += 444.

25 Example 508

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N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-1-[(2-methyl-4-quinolinyl)methyl]-1H-indole-4-carboxamide trifluoroacetate

(508a) Following a procedure analogous to that used in example (501) but using the methyl 2-aminocyclopentanecarboxylate and 1*H*-indole-4-carboxylic acid, the title compound (0.085 g. 56%) was prepared as a white amorphous solid, MS (M+H) += 443.

Example 700

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(700a) Chlorosulfonylisocyanate (4.80 g, 33.9 mmol) in methylene chloride (2 mL) was added dropwise to cycloheptene in methylene chloride (25 mL) then heated to reflux under nitrogen for 10 h. The reaction was quenched by dropwise addition of water then extracted with methylene chloride (2X). The combined organic layers were washed with water (1X) and brine (1X) then dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue diluted with ether (15 mL). The ether solution was added dropwise to a solution of 10% södium sulfite/ether (2:1, 75 mL) maintaining the pH between 7 and 8 with 10% sodium hydroxide. After the addition was complete stirring was continued for 0.5 h then the reaction was extracted with ether (3X). The combined organic layers were washed with water (1X) and brine (1X) then dried over magnesium sulfate. The solvent was evaporated in vacuo to provide 700a (3.76 g, 87%) as a waxy yellow solid. MS: APc [M+(CH₃CN+H)]⁺=181.

(700b) Chlorotrimethylsilane (5.87 g, 54 mmol) was added
25 dropwise to 700a (3.76 g, 27.0 mmol) in methanol (75 mL) at room temperature under nitrogen. After stirring for 2 h the solvent was evaporated in vacuo and the residue titurated with ether. The white solid was filtered then dried under vacuum for 24 h to provide 700b (4.52 g, 81%). MS: ESI
30 [M+H]*=172.

(700c) N-Methyl morpholine (0.73 g, 7.22 mmol) was added dropwise to 700b (0.5 g, 2.41 mmol), BOP reagent (1.17 g, 2.65 mmol), and 4-[(2-methyl-4-quinolinyl)methoxy]benzoic acid (0.71 g, 2.41 mmol) in dimethylformamide (10 mL) at 0°C

under nitrogen. The reaction was allowed to warm to room temperature then stirred overnight. The solvent was removed in vacuo and the residue taken up in ethyl acetate (100 mL). The solution was washed with water (2X), saturated sodium bicarbonate (2X), and brine (1X) then dried over magnesium sulfate. The solvent was removed in vacuo and the residue purified by flash chromatography (SiO₂, 75%-100% ethyl acetate/hexanes) to provide 700c (0.963 g, 89%) as a viscous light yellow oil. MS: ESI [M+H]⁺=447.

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(700d) A solution of basic hydroxylamine was prepared by adding potassium hydroxide (2.81g, 50.2 mmol) in methanol (7 mL) to hydroxylamine hydrochloride (2.34g, 33.7 mmol) in hot methanol (12 mL). The solution was allowed to cool to ambient temperature and the solid potassium chloride was filtered. The hydroxylamine solution (15 mL) was added in one portion to 700c (0.25g, 0.56 mmol) and stirred for 6 h. The reaction was quenched with 1N hydrogen chloride (~15 mL) until the pH was approximately 6. The solvent was removed in vacuo and the residue taken up in 1N hydrogen chloride/methanol (1:1) then purified by C₁₈ HPLC to provide example 700(88 mg, 32%). MS: ESI [M+H]*=448.

Example 701

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(701a) Diazabicyclo[5.4.0]undec-5-ene (0.39 g, 2.58 mmol)
30 was added to 700c(0.23 g, 0.52 mmol) in xylenes (10 mL) then
heated at 100°C for 8 h and 110°C for 14 h. The solvent was
evaporated in vacuo and the residue purified by flash
chromatography (SiO₂, 65% ethyl acetate/hexanes) to provide
701a (103 mg, 45%) with >90% isomeric purity. MS: ESI
35 [M+H]*=447.

(701b) Example 701 was prepared in a procedure analogous to 700d. MS: ESI [M+H]⁺=448.

5 **Example 702**

(4S,5R)-N-hydroxy-5-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-2-oxohexahydro-1H-azepine-4-carboxamide trifluoroacetate

- 10 (702a) Diphenylphosphoryl azide (4.72 g, 17.1 mmol) was added dropwise to 1-methyl (1S, 2R) - (+) - cis - 1, 2, 3, 6 tetrahydrophthalate (2.63 g, 14.3 mol) and triethylamine (2.17 g, 41.2 mmol) in benzene (20 mL) at room temperature. After stirring for 2 h benzyl alcohol (1.85 g, 17.1 mmol) 15 was added and the reaction was heated to reflux for 3 h. The mixture was cooled to room temperature and diluted with ethyl acetate (150 mL). The solution was washed with water (1X), 10% citric acid (1X), saturated sodium bicarbonate (1X), and brine (1X) then dried over magnesium sulfate. solvent was evaporated in vacuo and the residue purified by 20 flash chromatography (SiO₂, 20-30% ethyl acetate/hexanes as solvent. The product 702a (2.69, 65%) was isolated as a brittle foam. MS: ESI [M+H] += 290.
- 25 (702b) Borane:tetrahydrofuran (1M, 9.66 mL, 9.66 mmol) was added dropwise to 702a (2.15 g, 7.43 mmol) in anhydrous tetrahydrofuran (20 mL) at 0°C under nitrogen. The reaction was allowed to warm to room temperature over 1.5 h then cooled again to 0°C and quenched by the dropwise addition of a with of 30% hydrogen peroxide (4.5 mL) and 1N sodium hydroxide (10 mL). After the addition was completed the mixture was stirred 15 m then quenched with 10% sodium sulfite. The solution was extracted with ethyl acetate (3X) and the combined organic extracts were washed with 10% sodium sulfite (2X) and brine (1X). After drying over

magnesium sulfate the solvent was removed in vacuo and the product 702b (2.35 g, 100%) was carried forward without further purification. MS: APc [M+H]*=308.

- 5 (702c) Pyridinium dichromate (4.19 g. 11.1 mmol) was added in one portion to 702b(7.43 mmol) and powdered 3 Å molecular sieves (5 g) in methylene chloride (30 mL) then stirred for 3 h at ambient temperature. The reaction was filtered through celite under vacuum washing with methylene chloride.
- The solvent was evaporated *in vacuo* and the residue purified by flash chromatography (SiO₂, 50% ethyl acetate/hexanes) to provide 702c (1.68 g, 74%) as a viscous light yellow oil.

 MS: APc [M+H]⁺=306.
- 15 (702d) Hydroxylamine hydrochloride (1.53 g, 22.0 mmol) was added in one portion to 702c (1.68 g, 5.50 mmol) and sodium bicarbonate (1.53 g, 18.2 mmol) in methanol (25 mL) then heated to reflux for 3 h. The mixture was cooled to ambient temperature then diluted with water (50 mL) and extracted with chloroform (4X). The combined organic extracts were washed with brine (1X) then dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue purified by flash chromatography (SiO₂, 50% ethyl acetate/hexanes) to provide 702d (1.46 g, 83%) as a viscous light yellow oil.

 25 MS: ESI [M+H]*=321.
- (702e) 702d(1.46 g, 4.56 mmol) in methylene chloride (10 mL) was added dropwise to p-toluenesulfonyl chloride (1.04 g, 5.47 mmol) and pyridine (0.54 g, 6.84 mmol) in methylene chloride (20 mL) at room temperature. The reaction was stirred for 14 h then diluted with methylene chloride (80 mL). The solution was washed with 1N hydrochloric acid (2X), saturated sodium bicarbonate (2X), and brine (1X) then dried over magnesium sulfate. The solvent was evaporated in vacuo and the tosylate ([M+H]*=475) was taken up in ethanol

free chloroform (40 mL) and added to dry silica gel(20 g).

The reaction was stirred for 4 h then poured onto the top of a flash column (SiO₂, 80 g, 50%-ethyl acetate hexanes to 50% methanol/ethyl acetate) and eluted. The mixture of four regioisomeric lactams were purified by C₁₈ HPLC (CH₃CN/water, 0.1% trifluoroacetic acid) to provide 702e-a, 702e-b, 702e-c, and 702e-d (410 mg, 267 mg, 364, mg, 195 mg, respectively, 85%). MS: APC [M+H]*=321 for all samples.

- 10 (702f) Methanol (10 mL) was carefully added to 10% Pd on C (0.17 g) and 702e-c (264 mg, 1.14 mmol) under a bed of nitrogen. A hydrogen balloon was attached via a three-way stopcock and the atmosphere was removed and replaced with hydrogen three times. After 0.5 h the hydrogen was removed and replaced with nitrogen then the catalyst removed by vacuum filtration through celite. The solvent was removed in vacuo to provide 702f (239 mg, 100%) as a viscous oil. MS: ESI [M+H]⁺=187.
- 20 (702g) In a procedure analogous to 700c, 702f was coupled to 4-[(2-methyl-4-quinolinyl)methoxy]benzoic acid to provide 702g (0.28 g, 53%)as a viscous clear oil. MS: ESI [M+H]+=462.
- 25 (702h) In a procedure analogous to 700d, 702g was converted to the hydroxamic acid example 702 were the regiochemistry was proven by 2D ¹HNMR. MS: ESI [M+H] +=463.

Example 703 and Example 704

30 (3S,4S)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-7-oxohexahydro-1H-azepine-4-carboxamide trifluoroacetate and (3S,4R)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-7-oxohexahydro-1H-azepine-3-carboxamide trifluoroacetate and (4S,5R)-N-hydroxy-5-({4-[(2-methyl-4-

WO 01/70673 PCT/US01/08334 quinolinyl)methoxy]benzoyl}amino)-7-oxohexahydro-1H-azepine-4-carboxamide trifluoroacetate

(703a) In a series of procedures analogous to steps 702f through 702h, 702e-a was converted to example 703.

(704) In a series of procedures analogous to steps 702f through 702h 702e-b was converted example 704.

Example 705 and Example 706

 $(2S, 3R) - N - hydroxy - 3 - ({4 - {(2-methyl - 4 - {(2$

quinolinyl)methoxy]benzoyl}amino)-2-pyrrolidinecarboxamide ditrifluoroacetate and (2R,3R)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-2-pyrrolidinecarboxamide

ditrifluoroacetate

(705a,706a) Di-t-butyl dicarbonate (8.60 g, 39.4 mmol) in tetrahydrofuran (20 mL) was added dropwise to trans-3-hydroxy-L-proline (5.16 g, 39.4 mmol) in mixture of 1N sodium hydroxide (43.3 mL) and tetrahydrofuran (20 mL) at ambient temperature. The solution was stirred overnight then extracted with pet ether (2X). The pet ether extracts were washed with saturated sodium bicarbonate (3X) then the combined aqueous layers were carefully acidified with sodium hydrogensulfate monohydate. The aqueous solution was extracted with ethyl acetate (3X) and the combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo to give 706a/707a (8.29 g, 91%). MS: ESI-[M-H]=230.

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(705b,706b) N-Methyl morpholine (7.25 g, 71.7 mmol) was added in a slow stream to 705a,706a (8.29 g, 35.8 mmol), BOP reagent (17.4 g, 39.4 mmol), and N-benzylhydroxylamine hydrochloride (7.44 g, 46.6 mmol) in dimethylformamide (75 mL) under nitrogen. The reaction was stirred overnight and

the solvent was evaporated in vacuo. The residue was taken up in ethyl acetate (300 mL) and washed with water (2X), 10% citric acid (2X), saturated sodium bicarbonate (2X), and brine (1X) then dried over magnesium sulfate. The solvent was removed in vacuo and the residue purified by flash chromatography (SiO₂, 50%-80% ethyl acetate/hexanes) to provide 706b,707b(6.11 g, 51%) as a viscous oil. MS: ESI $[M+H]^{+}=337.$

- 10 (705c,706c) Diazoethyldicarboxylate (3.16 g, 18.2 mmol) was added dropwise to 705b,706b (6.11 g, 18.2 mmol) and triphenylphosphine (5.24 g, 20.0 mmol) in anhydrous tetrahydrofuran (50 mL) at room temperature under nitrogen. After stirring overnight the solvent was evaporated in vacuo 15 and the residue purified by flash chromatography (SiO2, 20%-30% ethyl acetate/hexanes) to provide 706c,707c (4.61 g, 80%). MS: APc $[M+H]^+=319$.
- (705d,706d) Methanol (75 mL) was carefully added to 20 705c,706c(4.61 g, 14.5 mmol) and Pd on C(10%, 1.3 g) under a bed of nitrogen. A hydrogen balloon was attached via a 3way stopcock and the atmosphere was removed and replace with hydrogen three times. After 1.5 h the hydrogen was removed and the reaction was vented with nitrogen. The catalyst was 25 removed by vacuum filtration through celite and the sovent was removed in vacuo to provide 706d,707d (3.09 g, 93%). MS: APC $\{M+H\}^{+}=229$.
- (705e, 706e) Sodium acetate (23.8 g, 290 mmol) was added to 30 705d,706d (3.09 g, 13.5 mmol) in water/tetrahydrofuran (200 mL, 1/1) at room temperature. Titanium trichloride (36.7 g, 12 wt% in 21% HCl(ag), 29.0 mmol) was added dropwise and stirring was continued for 3 h at room temperature. reaction mixture was extracted with ethyl acetate (1X) then
- 35 titanium dioxide was removed from the aqueous layer by

vacuum filtration through celite. The aqueous layer was extracted again with ethyl acetate (2X) and the combined ethyl acetate layers were washed with brine (1X). The solvent was removed *in vacuo* and the resulting solid was recrystallized from ethyl acetate/hexanes to provide 706e, 707e (1.64 g, 57%). MS: CI [(M-C₄H₈)+H]⁺=157.

(705f,706f) Chlorotrimethylsilane (256 mg, 2.36 mmol) was
added dropwise to 705e,706e (250 mg, 1.18 mmol) in methanol
(2 mL) at room temperature under nitrogen. After stirring
for 2 h the solvent was evaporated in vacuo and the residue
titurated with ether. The white solid was filtered then
dried under vacuum for 24 h to provide an inseparable
mixture of Boc protected β-amino acid and Boc deprotected βamino acid 706f,707f (235 mg) that was taken forward without
further purification. MS: CI [(M-NH₃)+H]⁺=128.

(705g,706g) In a procedure analogous to 700c, 705f,706f (281 mg) was coupled to 4-[(2-methyl-4-quinolinyl)methoxy]benzoic acid to provide 706g,707g-a(Boc deprotected, 78 mg, MS ESI: [M+H]⁺=420) and 706g,707g-b (Boc protected, 29 mg, [M+H]⁺=520).

(705h,706h) Examples 706 and 707 were prepared from 705g,706g-a using a procedure analogous to 700d. Example 707 was the first off the C₁₈ HPLC column(MS: ESI [M+H]⁺=421) and example 706 was the first (MS: ESI [M+H]⁺=421).

30 Example 707

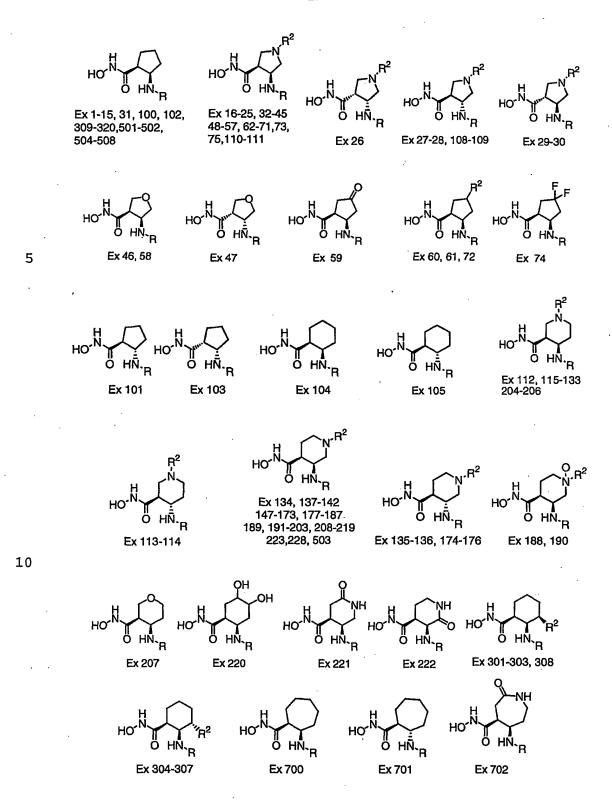
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tert-butyl (2S,3R)-2-[(hydroxyamino)carbonyl]-3-({4-[(2methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate trifluoroacetate

(707a) Example 707 was prepared from 705g,705g-b using a procedure analogous to 700d. Example 708 was isolated as a single diastereomer. MS: ESI [M+H]⁺=521.

Table 1



Ex	R	R ²	MS
15A	K	I.	[M+H]
1	4-(2-trifluoromethylphenyl)		393
_	benzoyl		333
2	4-(2-trifluoromethylphenoxy)		409
	benzoyl ·		305
3	4-(3-methyl-2-		340
	pyridinyl)benzoyl		340
4	4-phenylbenzoyl		325
5	4-phenoxybenzoyl		341
6	4-benzyloxybenzoyl		355
7	4-(2-methoxyphenyl)benzoyl		355
8	4-(2-methylphenyl)benzoyl		339
9	4-(2-methoxyphenoxy)benzoyl		371
10	4-(2-methylphenoxy)benzoyl	and Red	355
11	4-(3-methylphenyl)benzoyl	,	339
12	4-(4-quinolinyl)benzoyl	,	376
13	4-(3,5-		353
	dimethylphenyl)benzoyl		333
14	5-[2-(2-methylphenyl)]		340
1.4	pyridinylcarbonŷl		340
15	5-[2-(2-methoxyphenyl)]		356
1	pyridinylcarbonyl		336
16	4-(2-methyl-4-	Isopropyl	463
10	quinolinylmethoxy)benzoyl	Ισοριοργι	403
17	4-(2-methyl-4-	2,2-	505
1 1	quinolinylmethoxy)benzoyl	dimethylpropionyl	505
18	4-(2-methyl-4-	methanesulfonyl	499

32 d-(2-methyl-4- 1,1-dimethyl-2- quinolinylmethoxy)benzoyl propynyl 487		quinolinylmethoxy)benzoyl		Ţ <u>-</u>
Quinolinylmethoxy) benzoyl	19	4-(2-methyl-4-	Methyl	435
20 quinolinylmethoxy) benzoyl ethoxy) carbonyl 21		quinolinylmethoxy)benzoyl	-	433
quinolinylmethoxy) benzoyl	20	4-(2-methyl-4-	(1,1-dimethyl-	521
21 quinolinylmethoxy) benzoyl 22	20	quinolinylmethoxy)benzoyl	ethoxy)carbonyl	321
Quinolinylmethoxy) benzoyl 4-[N-(1,1-dimethyl-quinolinylmethoxy) benzoyl ethoxy) carbonyl piperidinyl 504	21	4-(2-methyl-4-	н	421
22		quinolinylmethoxy)benzoyl	1.	,=2.1
quinolinylmethoxy) benzoyl ethoxy) carbonyl] piperidinyl 4-(2-methyl-4-quinolinylmethoxy) benzoyl 4-(2-methyl-4-quinolinylmethoxy) benzoyl 24 quinolinylmethoxy) benzoyl 25 quinolinylmethoxy) benzoyl 26 quinolinylmethoxy) benzoyl 27 quinolinylmethoxy) benzoyl 28 quinolinylmethoxy) benzoyl 29 quinolinylmethoxy) benzoyl 3-[N-(1,1-dimethyl-ethoxy) carbonyl] pyrrolidinyl 4-(2-methyl-4-quinolinylmethoxy) benzoyl ethoxy) carbonyl 521 ethoxy) carbonyl 28 quinolinylmethoxy) benzoyl 29 quinolinylmethoxy) benzoyl 4-(2-methyl-4-quinolinylmethoxy) benzoyl 30 quinolinylmethoxy) benzoyl 4-(2-methyl-4-quinolinylmethoxy) benzoyl 31 quinolinylmethoxy) benzoyl 32 quinolinylmethoxy) benzoyl 33 quinolinylmethoxy) benzoyl 4-(2-methyl-4-quinolinylmethoxy) benzoyl 31 quinolinylmethoxy) benzoyl 32 quinolinylmethoxy) benzoyl 33 quinolinylmethoxy) benzoyl 4-(2-methyl-4-quinolinylmethoxy) benzoyl 4-(2-methyl-4-quinolinylmethoxy) benzoyl 34 quinolinylmethoxy) benzoyl 4-(2-methyl-4-quinolinylmethoxy) benzoyl			4-[N-(1,1-	-
quinolinylmethoxy) benzoyl ethoxy) carbonyl] piperidinyl 4-(2-methyl-4- quinolinylmethoxy) benzoyl 3-[N-(1,1- dimethyl- quinolinylmethoxy) benzoyl 24 quinolinylmethoxy) benzoyl 25 quinolinylmethoxy) benzoyl 26 quinolinylmethoxy) benzoyl 27 quinolinylmethoxy) benzoyl 28 quinolinylmethoxy) benzoyl 29 quinolinylmethoxy) benzoyl 30 quinolinylmethoxy) benzoyl 4-(2-methyl-4- quinolinylmethoxy) benzoyl 30 quinolinylmethoxy) benzoyl 31 quinolinylmethoxy) benzoyl 32 quinolinylmethoxy) benzoyl 33 quinolinylmethoxy) benzoyl 4-(2-methyl-4- quinolinylmethoxy) benzoyl 31 quinolinylmethoxy) benzoyl 32 quinolinylmethoxy) benzoyl 33 quinolinylmethoxy) benzoyl 34 quinolinylmethoxy) benzoyl 35 quinolinylmethoxy) benzoyl 36 quinolinylmethoxy) benzoyl 37 quinolinylmethoxy) benzoyl 38 quinolinylmethoxy) benzoyl 39 quinolinylmethoxy) benzoyl 30 quinolinylmethoxy) benzoyl 31 quinolinylmethoxy) benzoyl 32 quinolinylmethoxy) benzoyl 33 quinolinylmethoxy) benzoyl	22	4-(2-methyl-4-	dimethyl-	604
23		quinolinylmethoxy)benzoyl	ethoxy)carbonyl]	004
23 quinolinylmethoxy) benzoyl 4-piperidinyl 504 24 4-(2-methyl-4- dimethyl- quinolinylmethoxy) benzoyl ethoxy) carbonyl] pyrrolidinyl 590 25 4-(2-methyl-4- quinolinylmethoxy) benzoyl pyrrolidinyl 490 26 4-(2-methyl-4- quinolinylmethoxy) benzoyl (1,1-dimethyl- 521 ethoxy) carbonyl 521 27 4-(2-methyl-4- quinolinylmethoxy) benzoyl ethoxy) carbonyl 521 28 4-(2-methyl-4- quinolinylmethoxy) benzoyl H 421 29 4-(2-methyl-4- quinolinylmethoxy) benzoyl ethoxy) carbonyl 521 30 4-(2-methyl-4- quinolinylmethoxy) benzoyl H 421 31 4-(4-pyridinyl) benzoyl 326 32 4-(2-methyl-4- quinolinylmethoxy) benzoyl propynyl 487			piperidinyl	
24 4-(2-methyl-4- dimethyl- quinolinylmethoxy) benzoyl 3-[N-(1,1- dimethyl- pyrrolidinyl pyrrolidinyl 590 25 4-(2-methyl-4- quinolinylmethoxy) benzoyl pyrrolidinyl pyrrolidinyl 490 26 4-(2-methyl-4- quinolinylmethoxy) benzoyl ethoxy) carbonyl ethoxy) carbonyl 521 27 4-(2-methyl-4- quinolinylmethoxy) benzoyl ethoxy) carbonyl 521 28 4-(2-methyl-4- quinolinylmethoxy) benzoyl H 421 29 4-(2-methyl-4- quinolinylmethoxy) benzoyl ethoxy) carbonyl 521 30 4-(2-methyl-4- quinolinylmethoxy) benzoyl ethoxy) carbonyl 521 31 4-(4-pyridinyl)benzoyl H 421 31 4-(4-pyridinyl)benzoyl 326 32 quinolinylmethoxy) benzoyl propynyl 487	23	4-(2-methyl-4-	4-piperidinyl	504
24 4-(2-methyl-4- quinolinylmethoxy) benzoyl quinolinylmethoxy) benzoyl ethoxy) carbonyl pyrrolidinyl 590 25 4-(2-methyl-4- quinolinylmethoxy) benzoyl quinolinylmethoxy) benzoyl pyrrolidinyl 490 26 4-(2-methyl-4- quinolinylmethoxy) benzoyl ethoxy) carbonyl 521 27 4-(2-methyl-4- quinolinylmethoxy) benzoyl ethoxy) carbonyl 521 28 4-(2-methyl-4- quinolinylmethoxy) benzoyl H 421 29 4-(2-methyl-4- quinolinylmethoxy) benzoyl ethoxy) carbonyl 521 30 4-(2-methyl-4- quinolinylmethoxy) benzoyl h 421 31 4-(4-pyridinyl) benzoyl 326 32 4-(2-methyl-4- quinolinylmethoxy) benzoyl 1,1-dimethyl-2- quinolinylmethoxy) benzoyl 487		quinolinylmethoxy)benzoyl	a proceedings	304
quinolinylmethoxy)benzoyl ethoxy)carbonyl] pyrrolidinyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl pyrrolidinyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl ethoxy)carbonyl 26			3-[N-(1,1-	
quinolinylmethoxy) benzoyl ethoxy) carbonyl] pyrrolidinyl 25	2.4	4-(2-methyl-4-	dimethyl-	590
25 4-(2-methyl-4-quinolinylmethoxy) benzoyl pyrrolidinyl 490 26 4-(2-methyl-4-quinolinylmethoxy) benzoyl (1,1-dimethyl-ethoxy) carbonyl 521 27 4-(2-methyl-4-quinolinylmethoxy) benzoyl (1,1-dimethyl-ethoxy) carbonyl 521 28 4-(2-methyl-4-quinolinylmethoxy) benzoyl H 421 29 4-(2-methyl-4-quinolinylmethoxy) benzoyl (1,1-dimethyl-ethoxy) carbonyl 521 30 4-(2-methyl-4-quinolinylmethoxy) benzoyl H 421 31 4-(4-pyridinyl) benzoyl 326 32 4-(2-methyl-4-quinolinylmethoxy) benzoyl 1,1-dimethyl-2-quinolinylmethoxy) benzoyl 487		quinolinylmethoxy)benzoyl	ethoxy)carbonyl]	390
quinolinylmethoxy)benzoyl pyrrolidinyl 490 4-(2-methyl-4-quinolinylmethoxy)benzoyl ethoxy)carbonyl 27			pyrrolidinyl	
26 4-(2-methyl-4- quinolinylmethoxy) benzoyl ethoxy) carbonyl 521 27 4-(2-methyl-4- quinolinylmethoxy) benzoyl ethoxy) carbonyl 521 28 4-(2-methyl-4- quinolinylmethoxy) benzoyl ethoxy) carbonyl 421 29 4-(2-methyl-4- quinolinylmethoxy) benzoyl ethoxy) carbonyl 521 30 4-(2-methyl-4- quinolinylmethoxy) benzoyl ethoxy) carbonyl 521 31 4-(2-methyl-4- quinolinylmethoxy) benzoyl H 421 31 4-(4-pyridinyl) benzoyl 326 32 4-(2-methyl-4- quinolinylmethoxy) benzoyl 1,1-dimethyl-2- quinolinylmethoxy) benzoyl 487	25	4-(2-methyl-4-	pyrrolidinyl	490
quinolinylmethoxy)benzoyl ethoxy)carbonyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl ethoxy)carbonyl 28			pyriorramyr	100
quinolinylmethoxy)benzoyl ethoxy)carbonyl 27	26	4-(2-methyl-4-	(1,1-dimethyl-	521
quinolinylmethoxy)benzoyl ethoxy)carbonyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl 4-(4-pyridinyl)benzoyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl 1,1-dimethyl-2- quinolinylmethoxy)benzoyl 28 4-(2-methyl-4- quinolinylmethoxy)benzoyl 29 4-(2-methyl-4- quinolinylmethoxy)benzoyl 20 4-(2-methyl-4- quinolinylmethoxy)benzoyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl		quinolinylmethoxy)benzoyl	ethoxy)carbonyl	321
quinolinylmethoxy)benzoyl ethoxy)carbonyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl H 421 421 29 4-(2-methyl-4- quinolinylmethoxy)benzoyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl H 421 421 30 4-(2-methyl-4- quinolinylmethoxy)benzoyl 31 4-(4-pyridinyl)benzoyl 326 4-(2-methyl-4- quinolinylmethoxy)benzoyl propynyl	27	4-(2-methyl-4-	(1,1-dimethyl-	521
quinolinylmethoxy)benzoyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl H 421 421 30 4-(2-methyl-4- quinolinylmethoxy)benzoyl H 421 421 421 421 421 421 421		quinolinylmethoxy)benzoyl	ethoxy)carbonyl	321
quinolinylmethoxy) benzoyl 4-(2-methyl-4- quinolinylmethoxy) benzoyl 4-(2-methyl-4- quinolinylmethoxy) benzoyl H 421 30 4-(4-pyridinyl) benzoyl 4-(2-methyl-4- quinolinylmethoxy) benzoyl 31 4-(4-pyridinyl) benzoyl 4-(2-methyl-4- quinolinylmethoxy) benzoyl propynyl	28	4-(2-methyl-4-	H .	421
quinolinylmethoxy)benzoyl ethoxy)carbonyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl H 421 421 31 4-(4-pyridinyl)benzoyl 326 4-(2-methyl-4- quinolinylmethoxy)benzoyl propynyl	10.	quinolinylmethoxy)benzoyl	**	421
quinolinylmethoxy)benzoyl ethoxy)carbonyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl H 421 421 31 4-(4-pyridinyl)benzoyl 326 4-(2-methyl-4- quinolinylmethoxy)benzoyl propynyl 487	29	4-(2-methyl-4-	(1,1-dimethyl-	521
quinolinylmethoxy)benzoyl H 421 31 4-(4-pyridinyl)benzoyl 326 4-(2-methyl-4- 1,1-dimethyl-2- quinolinylmethoxy)benzoyl propynyl 487		quinolinylmethoxy)benzoyl	ethoxy)carbonyl	321
quinolinylmethoxy)benzoyl 31 4-(4-pyridinyl)benzoyl 326 4-(2-methyl-4- 1,1-dimethyl-2- 487 quinolinylmethoxy)benzoyl propynyl	30	4-(2-methyl-4-	н	421
32 4-(2-methyl-4- 1,1-dimethyl-2- quinolinylmethoxy)benzoyl propynyl 487		quinolinylmethoxy)benzoyl	"	721
quinolinylmethoxy)benzoyl propynyl 487	31	4-(4-pyridinyl)benzoyl		326
quinolinylmethoxy)benzoyl propynyl	. 32	4-(2-methyl-4-	1,1-dimethyl-2-	487
4-(2-methyl-4-		quinolinylmethoxy)benzoyl	propynyl	487
33 2-propynyl 459	33	4-(2-methyl-4-	2-propyny1	459
quinolinylmethoxy)benzoyl 2-propynyr 439		quinolinylmethoxy)benzoyl	z broblina.	=35

Γ	4-(2-methyl-4-	T	
34	quinolinylmethoxy)benzoyl	2-propenyl	461
	4-(2-methyl-4-		
35	quinolinylmethoxy)benzoyl	propyl	463
	4-(2-methyl-4-	2-methyl-2-	455
36	quinolinylmethoxy)benzoyl	propenyl	475
27	4-(2-methyl-4-	1,1-dimethyl-2-	400
37	quinolinylmethoxy)benzoyl	propenyl	489
38	4-(2-methyl-4-	1 1 4:	491
38	quinolinylmethoxy)benzoyl	1,1-dimethylpropyl	491
39	4-(2-methyl-4-	2 mathributer1	491
39	quinolinylmethoxy)benzoyl	3-methylbutyl	491
40	4-(2-methyl-4-	2,2-dimethylpropyl	491
40	quinolinylmethoxy)benzoyl	z,z-dimethyipiopyi	491
41	4-(2-methyl-4-	butyl	477
4	quinolinylmethoxy)benzoyl	Ducyr	477
42	4-(2-methyl-4-	3-butenyl	475
42	quinolinylmethoxy)benzoyl	1Villand-c	4/5
43	4-(2-methyl-4-	2-butynyl	473
40	quinolinylmethoxy)benzoyl	* Z Ducynyr	473
44	4-(2-methyl-4-	2-furylmethyl	501
4.4	quinolinylmethoxy)benzoyl	Z rury imeeny i	301
	4-(2-methyl-4-	(5-methyl-2-	F4.F
.45	quinolinylmethoxy)benzoyl	furyl)methyl	515
1.0	4-(2-methyl-4-		400
46	quinolinylmethoxy)benzoyl		422
47	4-(2-methyl-4-		422
47	quinolinylmethoxy)benzoyl		422
48	4-(2-methyl-4-	1,3-thiazol-2-	518
48	quinolinylmethoxy)benzoyl	ylmethyl	270
49	4-(2-methyl-4-	1, 2224-17	463
43	quinolinylmethoxy)benzoyl	acetyl	403
50	4-(2-methyl-4-	isobutyryl	491
30	quinolinylmethoxy)benzoyl	TSOUGCYTYT	
	<u> </u>		

51	505
4 /2 mothed 4	į
1 52 1	489
quinolinylmethoxy)benzoyl 1	
53 4-(2-methyl-4- cyclobutylcarbonyl quinolinylmethoxy)benzoyl	503
4-(2-methyl-4-	100
54 quinolinylmethoxy)benzoyl methoxyacetyl	493
4-(2-methyl-4- 55 2-furoyl	515
quinolinylmethoxy)benzoyl	213
4-(2-methyl-4- 56 2-thienylcarbonyl	531
quinolinylmethoxy)benzoyl	221
4-(2-methyl-4- 57 propionyl	477
quinolinylmethoxy)benzoyl	
58 4-(2-butynyloxy)benzoyl	319
59 4-(2-methyl-4-	434
quinolinylmethoxy)benzoyl	232
60 4-(2-methyl-4- OH	436
quinolinylmethoxy)benzoyl	120
61 4-(2-methyl-4- OH	436
quinolinylmethoxy)benzoyl	#30
62 4-(2-methyl-4- tetrahydro-2H-	505
quinolinylmethoxy)benzoyl pyran-4-yl	303
63 4-(2-methyl-4- methoxycarbonyl	479
quinolinylmethoxy)benzoyl	173
4-(2-methyl-4- 64 ethoxycarbonyl	493
quinolinylmethoxy)benzoyl	
4-(2-methyl-4- propyloxycarbonyl	507
quinolinylmethoxy)benzoyl	
4-(2-methyl-4-	
66	505
	ſ
67 4-(2-methyl-4- isopropyloxycarbon quinolinylmethoxy)benzoyl yl	507

68 4-(2-methyl-4-quinolinylmethoxy) benzoyl 2-propynyloxycarbony 50 69 4-(2-methyl-4-quinolinylmethoxy) benzoyl 2-butynyloxycarbonyl 51 70 4-(2-methyl-4-quinolinylmethoxy) benzoyl butenyloxycarbonyl 51 71 4-(2-methyl-4-quinolinylmethoxy) benzoyl benzyloxycarbonyl 55 72 4-(2-methyl-4-quinolinylmethoxy) benzoyl dimethylamino 46 73 4-(2-methyl-4-quinolinylmethoxy) benzoyl isopropyl 36 74 4-(2-methyl-4-quinolinylmethoxy) benzoyl isopropyl 39 75 4-(2-methyl-4-quinolinylmethoxy) benzoyl quinolinylmethoxyl benzoyl 42 101 4-(2-methyl-4-quinolinylmethoxyl benzoyl quinolinylmethoxyl benzoyl 42 102 4-(2-methyl-4-quinolinylmethoxyl benzoyl quinolinylmethoxyl benzoyl quinolinylmethoxyl benzoyl
quinolinylmethoxy) benzoyl butynyloxycarbonyl 4-(2-methyl-4- quinolinylmethoxy) benzoyl butenyloxycarbonyl 4-(2-methyl-4- quinolinylmethoxy) benzoyl benzyloxycarbonyl 55 72
quinolinylmethoxy) benzoyl butenyloxycarbonyl 4-(2-methyl-4- quinolinylmethoxy) benzoyl benzyloxycarbonyl 55 4-(2-methyl-4- quinolinylmethoxy) benzoyl dimethylamino 46 73
quinolinylmethoxy) benzoyl benzyloxycarbonyl 55 4-(2-methyl-4- quinolinylmethoxy) benzoyl dimethylamino 46 73 4-(2-butynyloxy) benzoyl isopropyl 36 74 quinolinylmethoxy) benzoyl isopropyl 39 75 4-(2-methyl-4- quinolinylmethoxy) benzoyl isopropyl 39 4-(2-methyl-4- quinolinylmethoxy) benzoyl 22 101 4-(2-methyl-4- quinolinylmethoxy) benzoyl
quinolinylmethoxy)benzoyl dimethylamino 46 73 4-(2-butynyloxy)benzoyl isopropyl 36 74 4-(2-methyl-4- quinolinylmethoxy)benzoyl isopropyl 39 75 4-(2-methyl-4- quinolinylmethoxy)benzoyl 42 100 4-(2-methyl-4- quinolinylmethoxy)benzoyl 42 101 4-(2-methyl-4- quinolinylmethoxy)benzoyl 42 102 4-(2-methyl-4- quinolinylmethoxy)benzoyl 42
74 4-(2-methyl-4- quinolinylmethoxy) benzoyl 45 75 4-(2-methylphenoxy) benzoyl isopropyl 39 100 4-(2-methyl-4- quinolinylmethoxy) benzoyl 42 101 4-(2-methyl-4- quinolinylmethoxy) benzoyl 42 102 4-(2-methyl-4- quinolinylmethoxy) benzoyl 42
quinolinylmethoxy) benzoyl isopropyl 39 4-(2-methyl-4- quinolinylmethoxy) benzoyl 42
100
quinolinylmethoxy)benzoyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl 42 42 42 42
quinolinylmethoxy)benzoyl 4-(2-methyl-4- quinolinylmethoxy)benzoyl 42
quinolinylmethoxy)benzoyl 42
4-(2-methyl-4- quinolinylmethoxy)benzoyl 42
104
105 4-(2-methyl-4- quinolinylmethoxy)benzoyl 43
108 4-(2-methyl-4- (1,1-dimethyl-quinolinylmethoxy)benzoyl ethoxy)carbonyl 52
109 4-(2-methyl-4- quinolinylmethoxy)benzoyl H 42:
110 4-(2-methyl-4- (1,1-dimethyl- carbonyl ethoxy)carbonyl 52:
111 4-(2-methyl-4- H 42:

	quinolinylmethoxy)benzoyl		
112	4-(2-methyl-4-	(1,1-dimethyl-	535
112	quinolinylmethoxy)benzoyl	ethoxy)carbonyl	333
113	4-(2-methyl-4-	(1,1-dimethyl-	535
113	quinolinylmethoxy)benzoyl	ethoxy)carbonyl	333
114	4-(2-methyl-4-	н	435
774	quinolinylmethoxy)benzoyl	11	#22
115	4-(2-methyl-4-	Н	435
	quinolinylmethoxy)benzoyl		433
116	4-(2-methyl-4-	butoxycarbonyl	535
110	quinolinylmethoxy)benzoyl	Ducoxycarbonyr	
117	4-(2-methyl-4-	(1-methyl-	521
	quinolinylmethoxy)benzoyl	ethoxy)carbonyl	321
118	4-(2-methyl-4-	methanesulfonyl	513
	quinolinylmethoxy)benzoyl	moondare are and a	313
119	4-(2-methyl-4-	benzenesulfonyl	575
	quinolinylmethoxy)benzoyl		0.0
120	4-(2-methyl-4-	acetyl	477
	quinolinylmethoxy)benzoyl		
121	4-(2-methyl-4-	benzoyl	539
	quinolinylmethoxy)benzoyl		
122	4-(2-methyl-4-	2,2-	519
	quinolinylmethoxy)benzoyl	dimethylpropionyl	
123	4-(2-methyl-4-	3,3-	533
	quinolinylmethoxy)benzoyl	dimethylbutanoyl	
124	4-(2-methyl-4-	4-	548
	quinolinylmethoxy)benzoyl	morpholinecarbonyl	
125	4-(2-methyl-4-	dimethylcarbamyl	506
	quinolinylmethoxy)benzoyl		
126	4-(2-methyl-4-	methyl	449
	quinolinylmethoxy)benzoyl	шеспут	
127	4-(2-methyl-4-	ethyl	463
	quinolinylmethoxy)benzoyl	3011,1	
128	4-(2-methyl-4-	n-propyl	477

Т	quinolinylmethoxy)benzoyl		·
	4-(2-methyl-4-		<u> </u>
129	quinolinylmethoxy)benzoyl	isopropyl	477
130	4-(2-methyl-4-		400
130	quinolinylmethoxy)benzoyl	cyclopropylmethyl	489
131	4-(2-methyl-4-	2,2-dimethylpropyl	505
	quinolinylmethoxy)benzoyl	2,2 and chytpropyr	303
132	4-(2-methyl-4-	-benzyl	525
132	quinolinylmethoxy)benzoyl	Delizyi) 525 _{. ,}
133	4-(2-methyl-4-	2 +hingolylmathyl	F20
133	quinolinylmethoxy)benzoyl	2-thiazolylmethyl	532
134	4-(2-methyl-4-	(1,1-dimethyl-	535
	quinolinylmethoxy)benzoyl	ethoxy) carbonyl	
135	4-(2-methyl-4-	(1,1-dimethyl-	535
	${\tt quinolinylmethoxy}) {\tt benzoyl}$	ethoxy)carbonyl	333
136	4-(2-methyl-4-	Н	435
130	quinolinylmethoxy)benzoyl		400
137	4-(2-methyl-4-	Н	435
13,	quinolinylmethoxy)benzoyl		433
138	4-(2-methyl-4-	(2-ethyl-	535
130	quinolinylmethoxy)benzoyl	propyloxy)carbonyl	333
139	4-(2-methy1-4-	methoxycarbonyl	493
	quinolinylmethoxy)benzoyl	meenoxy carbony r	400
140	4-(2-methyl-4-	(1-methyl-	521
	quinolinylmethoxy)benzoyl	ethoxy)carbonyl	321
141	4-(2-methyl-4-	methanesulfonyl	513
	quinolinylmethoxy)benzoyl	mechanesurionyi	313
142	4-(2-methyl-4-	benzenesulfonyl	575
742	quinolinylmethoxy)benzoyl	Denzenesdiionyi	373
147	4-(2-methyl-4-	3,3-	533
74/	quinolinylmethoxy)benzoyl	dimethylbutanoyl	222
148	4-(2-methyl-4-	2,2-	519
T#0	quinolinylmethoxy)benzoyl	dimethylpropionyl	
149	4-(2-methyl-4-	benzoyl	539

	quinolinylmethoxy)benzoyl		
150	4-(2-methyl-4-	nicotinoyl	540
130	quinolinylmethoxy)benzoyl	TITEOCITIOYI	340
151	4-(2-methyl-4-	2-	545
1 131	quinolinylmethoxy)benzoyl	thiophenecarbonyl	242
152	4-(2-methyl-4-	dimethylcarbamyl	-506
	quinolinylmethoxy)benzoyl	dimeeny rear bany r	300
153	4-(2-methyl-4-	4-	548
123	quinolinylmethoxy)benzoyl	morpholinecarbonyl	240
154	4-(2-methyl-4-	[2-(2-thienyl)	588
104	quinolinylmethoxy)benzoyl	ethyl]carbamyl	368
155	4-(2-methyl-4-	(1,1-dimethyl-	534·
133	quinolinylmethoxy)benzoyl ~	ethyl)carbamyl	234
156	4-(2-methyl-4-	Methyl	440
130	quinolinylmethoxy)benzoyl	Mecnyi	449
157	4-(2-methyl-4-	Ethyl	463
	quinolinylmethoxy)benzoyl	ECHYL	403
158	4-(2-methyl-4-	n-propyl	477
130	quinolinylmethoxy)benzoyl	H Propla	±//
159	4-(2-methyl-4-	isopropyl	477
	quinolinylmethoxy)benzoyl		4//
160	4-(2-methyl-4-	cyclobutyl	489
	quinolinylmethoxy)benzoyl ""	Cyclobacy1	400
161	4-(2-methyl-4-	n-butyl	491
	quinolinylmethoxy)benzoyl	11 24031	131
162	4-(2-methyl-4-	2-methylpropyl	491
	quinolinylmethoxy)benzoyl	a moengapaopga	
163	4-(2-methyl-4-	cyclopropylmethyl	489
	quinolinylmethoxy)benzoyl	cy dropropy micelly r	100
164	4-(2-methyl-4-	2,2-dimethylpropyl	505
202	quinolinylmethoxy)benzoyl		
165	4-(2-methyl-4-	cyclopentyl	503
100	quinolinylmethoxy)benzoyl	olorobench.	
166	4-(2-methyl-4-	4-	519

	quinolinylmethoxy)benzoyl	tetrahydropyranyl	1
ļ		cectanydropyranyr	
167	4-(2-methyl-4- quinolinylmethoxy)benzoyl	Benzyl	525 .
168	4-(2-methyl-4- quinolinylmethoxy)benzoyl	2-thiazolylmethyl	532
169	_ 4-(2-methyl-4- quinolinylmethoxy)benzoyl	4-picolyl	526
170	4-(2-methyl-4- quinolinylmethoxy)benzoyl	2-picolyl	526
171	4-(2-methyl-4- quinolinylmethoxy)benzoyl	3-picolyl	526
172	4-(2-methyl-4- quinolinylmethoxy)benzoyl	Trans-cinnamyl	551
173	4-(2-methyl-4- quinolinylmethoxy)benzoyl	Phenyl -	511
174	4-(2-methyl-4- quinolinylmethoxy)benzoyl	Pivolyl	519
175	4-(2-methyl-4- quinolinylmethoxy)benzoyl	Methyl	449
176	4-(2-methyl-4- quinolinylmethoxy)benzoyl	dimethylcarbamyl	506
177	4-(2-methyl-4- quinolinylmethoxy)benzoyl	_n-hexyl	519
178	4-(2-methyl-4- quinolinylmethoxy)benzoyl	2-fluoroethyl	481
179	4-(2-methyl-4- quinolinylmethoxy)benzoyl	2,2-difluoroethyl	499
180	4-(2-methyl-4- quinolinylmethoxy)benzoyl	1-methylpropyl	491
181	4-(2-methyl-4- quinolinylmethoxy)benzoyl	2-ethylpropyl	505
182	4-(2-methyl-4- quinolinylmethoxy)benzoyl	4-[N-(1,1- dimethyl- ethoxy)carbonyl]	618

Γ	,	piperidinyl	
		piperidinyi	
183	4-(2-methyl-4- quinolinylmethoxy)benzoyl	4-piperidinyl	518
		3-[N-(1,1-	
184	4-(2-methyl-4-	dimethyl-	604
104	quinolinylmethoxy)benzoyl	ethoxy)carbonyl]	004
		pyrrolidinyl	
105	4-(2-methyl-4-	P	F0F
185	quinolinylmethoxy)benzoyl	Pyrrolidinyl	505
100	4-(2-methyl-4-	1,1-dimethyl-2-	F 0.1
186	quinolinylmethoxy)benzoyl	propynyl	501
187	4-(2-methyl-4-	(3-	531
107	quinolinylmethoxy)benzoyl	thiophenyl)methyl	221
188	4-(2-methy1-4-	Isopropyl	493
100	quinolinylmethoxy)benzoyl	ISOPIOPYI	400
189	4-(2-methyl-1-oxo-4-	Isopropyl	493
103	quinolinylmethoxy)benzoyl	Isopropyi	4 23
190-	4-(2-methyl-1-oxo-4-	Isopropyl	509
	quinolinylmethoxy)benzoyl	150510531	509
191	4-(2-methyl-4-	2-oxo-2-(4-	562
471	quinolinylmethoxy)benzoyl	morpholinyl)ethyl	502
192	4-(2-methyl-4-	2-dimethylamino-2-	520
222	quinolinylmethoxy)benzoyl	oxoethyl	220
193	4-(2-methyl-4-	t-butylsulfonyl	555
100	quinolinylmethoxy)benzoyl	, c-bacy is all only i	, 555
194	4-(2-methyl-1-oxo-4-	t-butylsulfonyl	571
101	quinolinylmethoxy)benzoyl	c-bacy isaliony i	371
195	4-(2-methyl-4-	Benzenesulfonyl	575
100	quinolinylmethoxy)benzoyl	Denzenesurionyi	3/3
196	4-(2-methyl-4-	t-butylsulfinyl	539
	quinolinylmethoxy)benzoyl	t-DucyIsuIIInyI	
197	4-(2-methyl-4-	2-hydroxylethyl	479
	quinolinylmethoxy)benzoyl		
198	4-(2-methy1-4-	2-[(1,1-dimethyl-	578

<u> </u>	quinolinylmethoxy)benzoyl	ethoxy)carbonyl]	
ļ		aminoethyl	1
} <u>:</u> -	4-(2-methyl-4-		<u> </u>
199	quinolinylmethoxy)benzoyl	2-aminoethyl	47-8
		2-(N,N-	
200	4-(2-methyl-4-	dimethylamino)	506
	quinolinylmethoxy)benzoyl	ethyl	
<u> </u>	4-(2-methyl-4-	ecny 1	
201	quinolinylmethoxy)benzoyl	2-aminopropyl	492
	4-(2-methyl-4-	2-amino-3-	
202	· -		508
 	quinolinylmethoxy)benzoyl	hydroxypropyl	
	4-(2-methyl-4-	(2-	
203	quinolinylmethoxy)benzoyl	pyrrolidinyl) methy	518
<u> </u>		1	<u> </u>
204	4-(2-methyl-4-	2-hydroxylethyl	479
204	quinolinylmethoxy)benzoyl	2 mydroxyreemyr	4/9
205	4-(2-methyl-4-	2-aminoethyl	470
	quinolinylmethoxy)benzoyl		478
206	4-(2-methyl-4-	C1 -1	100
206	quinolinylmethoxy)benzoyl	Cyclobutyl	489
207	4-(2-methyl-4-		426
207	quinolinylmethoxy)benzoyl		436
200	- 4-(2-methyl-4-	A (1 1 1 1 1 1 1-	401
208	quinolinylmethoxy)benzoyl	tert-butyl	491
200	4-(2-methyl-4-	tert-butyloxy-2-	
209	quinolinylmethoxy)benzoyl	methylpropanoate	577
210	4-(2-methyl-4-	2-methylpropanoic	501
210	quinolinylmethoxy)benzoyl	acid	521
511	4-(2-methyl-4-	methyl-2-	F05
211	quinolinylmethoxy)benzoyl	methylpropanoate	535
	4-(2-methyl-4-	2-(4-morpholinyl)-	5.50
212	quinolinylmethoxy)benzoyl	2-oxoethyl	562
040	4-(2-methyl-4-	2-(dimethylamino)-	F20
213	quinolinylmethoxy)benzoyl	2-oxo	520
	<u> </u>	<u> </u>	لــــــا

WO 017		FC1/0801	100334
214	4-(2-methyl-4-	1,1-dimethyl-2-	503
	quinolinylmethoxy)benzoyl	propenyl	303
215	4-(2-methyl-4-	tert-pentyl	505
	quinolinylmethoxy)benzoyl	dere pencyr	303
216	4-(2-methyl-4-	2-propynyl	473
210	quinofinylmethoxy)benzoyl	Z-broblitt	4.73
217	4-(2-methyl-4-	2 proporti	475
21/	quinolinylmethoxy)benzoyl	2-propenyl	475
218	4-(2-methyl-4-	1-methyl-2-	407
210	quinolinylmethoxy)benzoyl	propynyl	487
219	4-(2-methyl-4-	1-methyl-2-	400
219	quinolinylmethoxy)benzoyl	propenyl	489
220	4-(2-methyl-4-		166
220	quinolinylmethoxy)benzoyl		466
221	4-(2-methy1-4-		140
221	quinolinylmethoxy)benzoyl		449
222	4-(2-methyl-4-		140
222	quinolinylmethoxy)benzoyl		449
223	4-(2-butynyloxy)benzoyl	isopropyl	374
224	4-(2-butynyloxy)benzoyl	Н	332
225	4-[(2-methyl-3-	(1,1-dimethyl-	405
	pyridinyl)methoxy]benzoyl	ethoxy) carbonyl	485
226	4-[(2-methyl-3-	7.7	3.05
220	pyridinyl)methoxy]benzoyl	H	385
227	4-(2,5-	(1,1-dimethyl-	406
221	dimethylbenzyl)oxy]benzoyl	ethoxy)carbonyl	496
228	4-(2,5-	TT	200
220	dimethylbenzyl)oxy]benzoyl}	Н	398
301	4-(2-methyl-4-	NITT	440
301	quinolinylmethoxy)benzoyl	NH_2	449
302	4-(2-methyl-4-		1.62
302	quinolinylmethoxy)benzoyl	NHMe	463
303	4-(2-methyl-4-	NMe ₂	477
	quinolinylmethoxy)benzoyl	7447.6.5	· · ·

WO 01/		PC1/US01	100334
304	4-(2-methyl-4-	NH ₂	449
	quinolinylmethoxy)benzoyl		
305	4-(2-methyl-4-	NMe ₂	477
	quinolinylmethoxy)benzoyl		
306	4-(2-methyl-4-	NH-i-Pr	491
	quinolinylmethoxy)benzoyl		
307	4-(2-methyl-4-	NHMe	463
30,	quinolinylmethoxy)benzoyl	INITIAE	463
308	4-(2-methy1-4-	OII	450
300	quinolinylmethoxy)benzoyl	OH	450
	4-{[(2-methyl-4-		419
309	quinolinyl)methyl]amino}		
	benzoyl		
	4-{methyl[(2-methyl-4-		
310	quinolinyl)methyl]amino}		. 433
	benzoyl		
311	4-(3-phenyl-4,5-dihydro-5-		304
1 277	isoxazolyl)benzoyl		394
312	4-[3-(4-pyridinyl)-4,5-		395
1 212	dihydro-5-isoxazolyl]benzoyl		
313	}-4-[3-(3-pyridinyl)-4,5-		205
213	dihydro-5-isoxazolyl]benzoyl		395
314	4-[3-(2-pyridiny1)-4,5-		205
1 214	dihydro-5-isoxazolyl]benzoyl		395
315	4-[3=(4-quinolinyl)-4,5-		445
313	dihydro-5-isoxazolyl]benzoyl		445
	4-[3-(2,6-Dimethyl-4-		 -
316	pyridinyl)-4,5-dihydro-5-		423
	isoxazolyl]benzoyl		
317	3-methoxy-4-[3-(4-		
	pyridinyl)-4,5-dihydro-5-		425
	isoxazolyl]benzoyl		
210	4-[3-(4-pyridinyl)-4,5-		42.1
318	dihydro-5-isoxazolyl]benzoyl		411

	0073	PC1/USV1/	00004
319	4-[5-(2-pyridinyl)-4,5-		395
	dihydro-3-isoxazolyl]benzoyl		
320	4-[5-(4-pyridinyl)-4,5-	· 	395
	dihydro-3-isoxazolyl]benzoyl		
	1-[(2-methyl-4-		
501	quinolinyl)methyl]-1H-	H	444
	indole-5-carbonyl	·	
	1-[(2-methyl-4-		
502	quinolinyl)methyl]-1H-		443
.	indole-5-carbonyl		
	6-[(2-methyl-4-		
503	quinolinyl)methoxy]-1-	н	485
	naphthoyl		
	6-[(2-methyl-4-		
504	quinolinyl)methoxy]-1-		4 70
	naphthoyl		
	6-[(2-methyl-4-		····
505	quinolinyl)methoxy]-2-		470
	naphthoyl	; .	
	6-[(2-methyl-4-		٠.
506	quinolinyl)methoxy]-1,2,3,4-		475
	tetrahydro-1-		475
	isoquinolinecarbonyl	,	
	1-[(2-methyl-4-		
507	quinolinyl)methyl]-1H-		444
;	benzimidazole-5-carbonyl		
	1-[(2-methyl-4-		
508	quinolinyl)methyl]-1H-		443
	indole-4-carboxamide		
701	4-(2-methyl-4-		448
,01	quinolinylmethoxy)benzoyl		440
702	4-(2-methyl-4-		463
/02	quinolinylmethoxy)benzoyl		#02
703	4-(2-methyl-4-		463

	quinolinylmethoxy)benzoyl		
704	4-(2-methyl-4- quinolinylmethoxy)benzoyl		463
705	4-(2-methyl-4- quinolinylmethoxy)benzoyl	Н	421
706	4-(2-methyl-4- quinolinylmethoxy)benzoyl	Н	421
707	4-(2-methyl-4- quinolinylmethoxy)benzoyl	(1,1-dimethyl- ethoxy)carbonyl	521

The following tables contain representative examples of the present invention. Each entry in each table is intended to be paired with each formula at the start of the table. For example, example 1 is intended to be paired with each of formulae A-AG.

Table 2

20

5

Ex #	R ¹⁰
1	Н
2	methyl
3	methoxy
4	1-methylethyl
5	1-methylethoxy
6	phenyl
7	[1,1'-biphenyl]-4-yl
8	phenoxy
9	2-phenylethyl
10	2-(3,5-dimethylphenyl)ethyl
11	1-(2,6-dimethylphenyl)ethyl
12	2-phenylethenyl
13	phenoxymethyl
14	(2-methylphenyl)methoxy
15	(3-methylphenyl)methoxy
16	3-methylphenoxy
17	2,6-dimethylphenoxy
18	(2,6-dimethylphenyl)methoxy
19	3,5-dimethylphenoxy
20	- (3,5-dimethylphenyl)methoxy
21	2-(3,5-dimethylphenyl)ethyl
22	2-(3,5-dimethylphenyl)ethenyl

23	(3-amino-5-methylphenyl)methoxy
24	(2-amino-6-methylphenyl)methoxy
25	(3-cyano-5-methylphenyl)methoxy
26	(3-cyano-5-methylphenoxy)methyl
27	(3-cyano-5-nitrophenyl)methoxy
28	(3,5-diethoxyphenyl)methoxy
29	(3,5-dimethoxyphenyl)methoxy
30	3,5-dimethoxyphenoxy
31	2-(3,5-dimethoxyphenyl)ethyl
32	1-(3,5-dimethoxyphenyl)ethoxy
33	(3,5-dichlorophenyl)methoxy
34	(2,6-dichlorophenyl)methoxy
35	(3,5-dibromophenyl)methoxy
36	3,5-dibromophenoxy
37	(3-amino-5-cyanophenyl)methoxy
38	[2,6-bis(trifluoromethyl)phenyl]methoxy
39	2,6-bis(trifluoromethyl)phenoxy
40	(3-aminocarbonyl-5-methylphenyl)methoxy
41	([1,1'-biphenyl]-2-yl)methoxy
42	([1,1'-biphenyl]-3-yl)methoxy
43	[5-methyl-3-(methylsulfonyl)phenyl]methoxy
44	5-methyl-3-(methylsulfonyl)phenoxy
45	(2-pyridinyl)methoxy
46	(4-pyridinyl)methoxy
47	(2,6-dimethyl-4-pyridinyl)methoxy
48	2,6-dimethyl-4-pyridinyloxy
49	1-(2,6-dimethyl-4-pyridinyl)ethoxy
50	(3,5-dimethyl-4-pyridinyl)methoxy
51	(2,6-diethyl-4-pyridinyl)methoxy
52	(2,6-dichloro-4-pyridinyl)methoxy
53	(2,6-dimethoxy-4-pyridinyl)methoxy
54	(2-chloro-6-methyl-4-pyridinyl)methoxy
55	(2-chloro-6-methoxy-4-pyridinyl)methoxy
56	(2-methoxy-6-methyl-4-pyridinyl)methoxy

57	(1-naphthalenyl)methoxy
58	1-naphthalenyloxy
59	(2-naphthalenyl)methoxy
60	(2-methyl-1-naphthalenyl)methoxy
61	(4-methyl-2-naphthalenyl)methoxy
62	(4-quinolinyl)methoxy
63	1-(4-quinolinyl)ethoxy
64	4-quinolinyloxy
65	(4-quinolinyloxy)methyl
66	2-(4-quinolinyl)ethyl
67	(2-methyl-4-quinolinyl)methoxy
68	2-methyl-4-quinolinyloxy
69	(2-chloro-4-quinolinyl) methoxy
70	(2-methoxy-4-quinolinyl)methoxy
71	(2-hydroxy-4-quinoliny1)methoxy
72	(2-trifluoromethyl-4-quinolinyl)methoxy
73	(2-phenyl-4-quinolinyl)methoxy
74	(2,6-dimethyl-4-quinolinyl)methoxy
75	(2,7-dimethyl-4-quinolinyl)methoxy
76	(5-quinolinyl)methoxy
77	(7-methyl-5-quinolinyl)methoxy
78	(7-methoxy-5-quinolinyl)methoxy
79	(8-quinolinyl)methoxy
80	2-(1,2,3-benzotriazol-1-yl)ethyl
81	(2-benzimidazolyl)methoxy
82	(1,4-dimethyl-5-imidazolyl)methoxy
83	(3,5-dimethyl-4-isoxazolyl)methoxy
84	(4,5-dimethyl-2-oxazolyl)methoxy
85	(2,5-dimethyl-4-thiazolyl)methoxy
86	(3,5-dimethyl-1-pyrazolyl)ethyl
87	(1,3-benzodioxo-4-yl)methoxy
88	(1,3,5-trimethyl-4-pyrazolyl)methoxy
89 .	(2,6-dimethyl-4-pyrimidinyl)methoxy
90	(4,5-dimethyl-2-furanyl)methoxy

91	(4,5-dimethyl-2-thiazolyl)methoxy
92	2-(2-oxazolyl)ethyl
93	2-butynyloxy
94	4-hydroxy-2-butynyloxy
95	4=pyridyl
96	4-pyridoxy
97	(2-methyl-4-quinolinyl)methylamino
98	3-phenyl-4,5-dihydro-5-isoxazolyl
99	3-(4-pyridinyl)-4,5-dihydro-5-isoxazolyl
100	5-(4-pyridinyl)-4,5-dihydro-3-isoxazolyl

Table 3

	HO N HN A	HO-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N	HO-H-H-N-H2
5	HO-N HN HN P	HO-N-H-2 N HO-N-H-2 E	HO-N-P2
	HO-N-R2-MA	HO HIN HS	HO-HIN-HIP-O-N
	HO HN H2	HO-HO-N-R ²	HO-HI HIN HIP PROPERTY OF THE
10	HO HN H	HO-HO-HO-NE N	0
	HO HIN P	HO HIN Q	HO N HN N
	Ex #	R ²	
	1	H	
	2	methyl	·
	3	ethyl	
	4	1-methylethyl	

1770070	1 C1/0301/
5	cyclobutyl
6	n-butyl
7	2,2-dimethylpropyl
8	cyclopropylmethyl
9	2-methoxyethyl
10	2-hydroxyethyl
11	2-aminoethyl
12	2-dimethylaminoethyl
13	2-(4-morpholinyl)ethyl
14	2-(1-piperidinyl)ethyl
15	2-(1-piperizinyl)ethyl
16	phenyl
17	benzyl
18	3-picolyl
19 .	formyl
20	acetyl
21	pivaloyl
22	benzoyl
23	nicotinoyl
24	methanesulfonyl
25	benzenesulfonyl
26	. t-butylsulfonyl
27	methoxycarbonyl
28	t-butoxycarbonyl
29	isopropyloxycarbonyl
30	Dimethylcarbamyl
31	4-morpholinecarbonyl
32	2-thiophenecarbonyl
33	2-fluoroethyl
34	2,2-difluoroethyl
35	2-(dimethylamino)-2-oxoethyl
36	2-oxo-2-(4-morphorlinyl)ethyl
37	tert-butyl
38	1,1-dimethylpropyl

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39	2-propenyl	
40	1-methyl-2-propenyl	
41	1,1-dimethyl-2-propenyl	
42	2-propynyl	 _
43	1-methyl-2-propynyl	
44	1,1-dimethyl-2-propynyl	
45	(2-pyrrolidinyl)methyl	<u> </u>

WO 01/70673 PCT/US01/08334 UTILITY

The compounds of formula I are expected to possess matrix metalloprotease and/or aggrecanase and/or TNF-α inhibitory activity. The MMP inhibitory activity of the 5 compounds of the present invention is demonstrated using assays of MMP activity, for example, using the assay described below for assaying inhibitors of MMP activity. The compounds of the present invention are expected to be bioavailable in vivo as demonstrated, for example, using the ex vivo assay described below. The compounds of formula I are expected to have the ability to suppress/inhibit cartilage degradation in vivo, for example, as demonstrated using the animal model of acute cartilage degradation described below.

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15 The compounds provided by this invention should also be useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit MPs. These would be provided in commercial kits comprising a compound of this invention.

20 Metalloproteases have also been implicated in the degradation of basement membranes to allow infiltration of cancer cells into the circulation and subsequent penetration into other tissues leading to tumor metastasis (Stetler-Stevenson, Cancer and Metastasis Reviews, 9, 289-303, 1990). 25 The compounds of the present invention should be useful for the prevention and treatment of invasive tumors by inhibition of this aspect of metastasis.

The compounds of the present invention should also have utility for the prevention and treatment of osteopenia associated with matrix metalloprotease-mediated breakdown of cartilage and bone that occurs in osteoporosis patients.

Compounds that inhibit the production or action of TNF and/or Aggrecanase and/or MMP's are potentially useful for the treatment or prophylaxis of various inflammatory, infectious, immunological or malignant diseases or

conditions. Thus, the present invention relates to a method of treating various inflammatory, infectious, immunological or malignant diseases. These include acute infection, acute phase response, age related macular degeneration,

- alcoholism, anorexia, asthma, autoimmune disease, autoimmune hepatitis, Bechet's disease, cachexia (including cachexia resulting from cancer or HIV), calcium pyrophosphate dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary
- disease, coagulation, congestive heart failure, corneal ulceration, Crohn's disease, enteropathic arthropathy (including inflammatory bowl disease), Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid withdrawal syndrome, gout, graft versus host
- disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation, intermittent hydrarthrosis, Lyme disease, meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease,
- 20 periodontitis, polymyositis/dermatomyositis, post-ischaemic reperfusion injury, post-radiation asthenia, psoriasis, psoriatic arthritis, pydoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis (including juvenile rheumatoid
- arthritis and adult rheumatoid arthritis), sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and tumor invasion by secondary metastases, spondylitis, stroke, systemic lupus erythematosus,
- 30 ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis.

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Some compounds of the present invention have been shown to inhibit TNF production in lipopolysacharride stimulated mice, for example, using the assay for TNF induction in mice and in human whole blood as described below.

Some compounds of the present invention have been shown to inhibit aggrecanase, a key enzyme in cartilage breakdown, as determined by the aggrecanase assay described below.

As used herein "µg" denotes microgram, "mg" denotes milligram, "g" denotes gram, "µL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, "µM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar and "nm" denotes nanometer. "Sigma stands for the Sigma-Aldrich Corp. of St. Louis, MO.

A compound is considered to be active if it has an IC50 or K_i value of less than about 10 μM for the inhibition of a desired MP. Preferred compounds of the present invention have K_i's or IC50's of ≤1 μM. More preferred compounds of the present invention have K_i's or IC50's of ≤0.1 μM. Even more preferred compounds of the present invention have K_i's or IC50's of ≤0.01 μM. Still more preferred compounds of the present invention have K_i's or IC50's of <0.001 μM.

Aggrecanase Enzymatic Assay

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A novel enzymatic assay was developed to detect potential inhibitors of aggrecanase. The assay uses active aggrecanase accumulated in media from stimulated bovine nasal cartilage (BNC) or related cartilage sources and purified cartilage aggrecan monomer or a fragment thereof as a substrate.

The substrate concentration, amount of aggrecanases time of incubation and amount of product loaded for Western analysis were optimized for use of this assay in screening putative aggrecanase inhibitors. Aggrecanase is generated by stimulation of cartilage slices with interleukin-1 (IL-1), tumor necrosis factor alpha (TNF- α) or other stimuli. Matrix metalloproteases (MMPs) are secreted from cartilage in an inactive, zymogen form following stimulation, although active enzymes are present within the matrix. We have shown

WO 01/70673 PCT/US01/08334 that following depletion of the extracellular aggrecan matrix, active MMPs are released into the culture media (Tortorella, M.D. et. al. Trans. Ortho. Res. Soc. 20, 341, 1995). Therefore, in order to accumulate BNC aggrecanase in culture media, cartilage is first depleted of endogenous aggrecan by stimulation with 500 ng/ml human recombinant ILß for 6 days with media changes every 2 days. Cartilage is then stimulated for an additional 8 days without media change to allow accumulation of soluble, active aggrecanase 10 in the culture media. In order to decrease the amount of other matrix metalloproteases released into the media during aggrecanase accumulation, agents which inhibit MMP-1, -2, -3, and -9 biosynthesis are included during stimulation. This BNC conditioned media, containing aggrecanase activity is then used as the source of aggrecanase for the assay. Aggrecanase enzymatic activity is detected by monitoring production of aggrecan fragments produced exclusively by cleavage at the Glu373-Ala374 bond within the aggrecan core protein by Western analysis using the monoclonal antibody, -BC-3 (Hughes, CE, et al., Biochem J 306:799-804, 1995). 20 This antibody recognizes aggrecan fragments with the Nterminus, 374ARGSVIL, generated upon cleavage by aggrecanase. The BC-3 antibody recognizes this necepitope only when it is at the N-terminus and not when it is present internally within aggrecan fragments or within the aggrecan 25 protein core. Other proteases produced by cartilage in response to IL-1 do not cleave aggrecan at the Glu373-Ala374 aggrecanase site; therefore, only products produced upon cleavage by aggrecanase are detected. Kinetic studies using

To evaluate inhibition of aggrecanase, compounds are prepared as 10 mM stocks in DMSO, water or other solvents and diluted to appropriate concentrations in water. Drug (50 ul) is added to 50 ul of aggrecanase-containing media and 50 ul of 2 mg/ml aggrecan substrate and brought to a

this assay yield a Km of 1.5 +/- 0.35 uM for aggrecanase.

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final volume of 200 ul in 0.2 M Tris, pH 7.6, containing 0.4 M NaCl and 40 mM CaCl₂. The assay is run for 4 hr at 37°C, quenched with 20 mM EDTA and analyzed for aggrecanasegenerated products. A sample containing enzyme and substrate without drug is included as a positive control and enzyme incubated in the absence of substrate serves as a measure of background.

Removal of the glycosaminoglycan side chains from aggrecan is necessary for the BC-3 antibody to recognize the ARGSVIL epitope on the core protein. Therefore, for 10 analysis of aggrecan fragments generated by cleavage at the Glu373-Ala374 site, proteoglycans and proteoglycan fragments are enzymatically deglycosylated with chondroitinase ABC (0.1 units/10 ug GAG) for 2 hr at 37°C and then with keratanase (0.1 units/10 ug GAG) and keratanase II (0.002 units/10 ug GAG) for 2 hr at 37°C in buffer containing 50 mM sodium acetate, 0.1 M Tris/HCl, pH 6.5. After digestion, aggrecan in the samples is precipitated with 5 volumes of acetone and resuspended in 30 ul of Tris glycine SDS sample buffer (Novex) containing 2.5% beta mercaptoethanol. 20 Samples are loaded and then separated by SDS-PAGE under reducing conditions with 4-12% gradient gels, transferred to nitrocellulose and immunolocated with 1:500 dilution of antibody BC3. Subsequently, membranes are incubated with a 1:5000 dilution of goat anti-mouse IgG alkaline phosphatase 25 second antibody and aggrecan catabolites visualized by incubation with appropriate substrate for 10-30 minutes to achieve optimal color development. Blots are quantitated by scanning densitometry and inhibition of aggrecanase determined by comparing the amount of product produced in 30 the presence versus absence of compound.

TNF PBMC ASSAY

Human peripheral blood mononuclear cells (PBMC) were obtained from normal donor blood by leukophoresis and

isolated by Ficoll-Paque density separation. PBMCs were suspended in .5ml RPMI 1640 with no serum at 2 x 10⁶ cells/ml in 96 well polystyrene plates. Cells were preincubated 10 minutes with compound, then stimulated with 1 µg/ml LPS (Lipopolysaccharide, Salmonella typhimurium) to induce TNF production. After an incubation of 5 hours at 37°C in 95% air, 5% CO₂ environment, culture supernatants were removed and tested by standard sandwich ELISA for TNF production.

10 TNF Human Whole Blood Assay

Blood is drawn from normal donors into tubes containing 143 USP units of heparin/10ml. 225ul of blood is plated directly into sterile polypropylene tubes. Compounds are diluted in DMSO/serum free media and added to the blood samples so the final concentration of compounds are 50, 10, 15 5, 1, .5, .1, and .01 µM. The final concentration of DMSO does not exceed .5%. Compounds are preincubated for 15 minutes before the addition of 100ng/ml LPS. Plates are incubated for 5 hours in an atmosphere of 5% CO2 in air. At the end of 5 hours, 750ul of serum free media is added to 20 each tube and the samples are spun at 1200RPM for 10 minutes. The supernatant is collected off the top and assayed for TNF-alpha production by a standard sandwich ELISA. The ability of compounds to inhibit TNF-alpha production by 50% compared to DMSO treated cultures is given 25 by the IC50 value.

TNF Induction In Mice

Test compounds are administered to mice either I.P. or

P.O. at time zero. Immediately following compound
administration, mice receive an I.P. injection of 20 mg of
D-galactosamine plus 10 µg of lipopolysaccharide. One hour
later, animals are anesthetized and bled by cardiac
puncture. Blood plasma is evaluated for TNF levels by an

ELISA specific for mouse TNF. Administration of

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representative compounds of the present invention to mice results in a dose-dependent suppression of plasma TNF levels at one hour in the above assay.

5 MMP ASSAYS

The enzymatic activities of recombinant MMP-1, 2, 3, 7, 8, 9, 13, 14, 15, and 16 were measured at 25°C with a fluorometric assay (Copeland, R.A.; Lombardo, D.; Giannaras, J. and Decicco, C.P. Bioorganic Med. Chem. Lett. 1995, 5, 10 1947-1952). Final enzyme concentrations in the assay were between 0.05 and 10 nM depending on the enzyme and the potency of the inhibitor tested. The permisive peptide substrate, MCA-Pro-Leu-Gly-Leu-DPA-Ala-Arg-NH2, was present at a final concentration of 10 uM in all assays. Initial 15 velocities, in the presence or absence of inhibitor, were measured as slopes of the linear portion of the product progress curves. IC50 values were determined by plotting the inhibitor concentration dependence of the fractional velocity for each enzyme, and fitting the data by non-linear 20 least squares methods to the standard isotherm equation (Copeland, R.A. Enzymes: A practical Introduction to Structure, Mechanism and Data Analysis, Wiley-VHC, New York, 1996, pp 187-223). All of the compounds studied here were assumed to act as competitive inhibitors of the enzyme, binding to the active site Zn atom as previously demonstrated by crystallographic studies of MMP-3 complexed with related hydroxamic acids (Rockwell, A.; Melden, M.; Copeland, R.A.; Hardman, K.; Decicco, C.P. and DeGrado, W.F. J. Am. Chem. Soc. 1996, 118, 10337-10338). Based on the 30 assumption of competitive inhibiton, the IC50 values were converted to Ki values as previously described.

Compounds tested in the above assay are considered to be active if they exhibit a K_i of $\leq 10~\mu M$. Preferred compounds of the present invention have K_i 's of $<1~\mu M$. More

preferred compounds of the present invention have K_i 's of $\leq 0.1~\mu\text{M}$. Even more preferred compounds of the present invention have K_i 's of $\leq 0.01~\mu\text{M}$. Still more preferred compounds of the present invention have K_i 's of $\leq 0.001~\mu\text{M}$.

Using the methodology described above, a number of compounds of the present invention were found to exhibit $K_{\underline{i}}$'s of <10 μM , thereby confirming the utility of the compounds of the present invention.

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Dosage and Formulation

The compounds of the present invention can be administered orally using any pharmaceutically acceptable dosage form known in the art for such administration. The active ingredient can be supplied in solid dosage forms such as dry powders, granules, tablets or capsules, or in liquid dosage forms, such as syrups or aqueous suspensions. The active ingredient can be administered alone, but is generally administered with a pharmaceutical carrier. A valuable treatise with respect to pharmaceutical dosage forms is Remington's Pharmaceutical Sciences, Mack Publishing.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an antiinflammatory and antiarthritic agent.

The compounds of this invention can be administered by any means that produces contact of the active agent with the agent's site of action in the body of a mammal. They can be

administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

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20 By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 25 mg/kg/day. For a normal male adult human of approximately 70 kg of body weight, this translates into a dosage of 70 to 1400 mg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the 30 present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those

forms of transdermal skin patches wall known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as carrier materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

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For instance, for oral administration in the form of a 15 tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral 20 administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable 25 binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium 30 alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch,

methyl cellulose, agar, bentonite, xanthan gum, and the like.

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The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamallar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues.

Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition. The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose

derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract. Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field. Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

30 Capsules

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Capsules are prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 100 milligrams of cellulose and 10 milligrams of magnesium stearate.

A large number of unit capsules may also prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Syrup

	<u> </u>	
		Wt. 8
	Active Ingredient	10
10	Liquid Sugar	50
	Sorbitol	20
	Glycerine	5
	Flavor, Colorant and	as required
	Preservative	
15	Water	as required

The final volume is brought up to 100% by the addition of distilled water.

20	•	Aqueous Suspension		
			•	Wt. %
		Active Ingredient		10
		Sodium Saccharin		0.01
		Keltrol® (Food Grade Xanthan	Gum)	0.2
25		Liquid Sugar	•	5
		Flavor, Colorant and	as	required
	•	Preservative		
		Water	as	required

Xanthan gum is slowly added into distilled water 30 before adding the active ingredient and the rest of the formulation ingredients. The final suspension is passed through a homogenizer to assure the elegance of the final products.

Resuspendable Powder

		•	<u>₩t. %</u>
		Active Ingredient	50.0
5		Lactose	35.0
·		Sugar	10.0
		Acacia	4.7
		Sodium Carboxylmethylcellulose	0.3
	Each	ingredient is finely pulverized	and then

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uniformly mixed together. Alternatively, the powder can be prepared as a suspension and then spray dried.

Semi-Solid Gel

15		₩t. %
	Active Ingredient	10
	Sodium Saccharin	0.02
,	Gelatin	2
	Flavor, Colorant and	as required
20	Preservative	
	Water	as required

Gelatin is prepared in hot water. The finely pulverized active ingredient is suspended in the gelatin solution and then the rest of the ingredients are mixed in. The suspension is filled into a suitable packaging container and cooled down to form the gel.

Semi-Solid Paste

•		Wt. &
	Active Ingredient	10
	Gelcarin® (Carrageenin gum)	1
5	Sodium Saccharin	0.01
	Gelatin	2
	Flavor, Colorant and	as required
	Preservative	
	Water	as required

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Gelcarin® is dissolved in hot water (around 80°C) and then the fine-powder active ingredient is suspended in this solution. Sodium saccharin and the rest of the formulation ingredients are added to the suspension while it is still warm. The suspension is homogenized and then filled into suitable containers.

Emulsifiable Paste

20		<u>Wt. 8</u>
	Active Ingredient	30
	Tween® 80 and Span® 80	6
	Keltrol®	0.5
	Mineral Oil	63.5

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All the ingredients are carefully mixed together to make a homogenous paste.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose and 10 milligrams of magnesium stearate.

A large number of tablets may also be prepared by conventional procedures so that the dosage unit was 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

15 Injectable

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A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension is-prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

The compounds of the present invention may be administered in combination with a second therapeutic agent, especially non-steroidal anti-inflammatory drugs (NSAID's). The compound of Formula I and such second therapeutic agent can be administered separately or as a physical combination in a single dosage unit, in any dosage form and by various routes of administration, as described above.

The compound of Formula I may be formulated together with the second therapeutic agent in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.). When the compound of Formula I and the second therapeutic agent are not formulated together in a single dosage unit, the compound of Formula I and the second therapeutic agent may be administered essentially at the same time, or in any order; for example the compound of Formula I may be administered first, followed by administration of the second agent. When not administered at the same time, preferably the administration of the compound of Formula I and the second therapeutic agent occurs less than about one hour apart, more preferably less than about 5 to 30 minutes apart.

Preferably the route of administration of the compound of Formula I is oral. Although it is preferable that the compound of Formula I and the second therapeutic agent are both administered by the same route (that is, for example, both orally), if desired, they may each be administered by different routes and in different dosage forms (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously).

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The dosage of the compound of Formula I when administered alone or in combination with a second therapeutic agent may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the

compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract 10 such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a sustainedrelease material which effects a sustained-release throughout the gastrointestinal tract and also serves to 15 minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination 20 product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to 25 further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of osteoarthritis or rheumatoid arthritis, which comprise one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

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In the present disclosure it should be understood that the specified materials and conditions are important in practicing the invention but that unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

WHAT IS CLAIMED IS:

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1. A compound of formula I:

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or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

A is selected from $-COR^5$, $-CO_2H$, CH_2CO_2H , $-CO_2R^6$, -CONHOH, $-CONHOR^5$, $-CONHOR^6$, $-N(OH)COR^5$, -N(OH)CHO, -SH, $-CH_2SH$, $-S(O)(=NH)R^a$, $-SN_2H_2R^a$, $-PO(OH)_2$, and $-PO(OH)NHR^a$;

ring B is a 3-13 membered non-aromatic carbocyclic or heterocyclic ring comprising: carbon atoms, 0-3 carbonyl groups, 0-4 double bonds, and from 0-2 ring heteroatoms selected from 0, N, NR², and S(0)_p, provided that ring B contains other than a S-S, 0-O, or S-O bond;

- Z is absent or selected from a C₃₋₁₃ carbocycle substituted

 with 0-5 R^b and a 5-14 membered heterocycle comprising:
 carbon atoms and 1-4 heteroatoms selected from the
 group consisting of N, O, and S(O)_p and substituted

 with 0-5 R^b;
- 25 U^a is absent or is selected from: 0, NR^{a^1} , C(0), C(0)0, OC(0), C(0)N R^{a^1} , NR^{a^1} C(0), OC(0)0, OC(0)N R^{a^1} , NR^{a^1} C(0)0, NR^{a^1} , $S(0)_D$, $S(0)_D NR^{a^1}$, NR^{a^1} S(0) $_D$, and NR^{a^1} S02 NR^{a^1} ;
- X^a is absent or selected from C_{1-10} alkylene, C_{2-10} 30 alkenylene, and C_{2-10} alkynylene;

 Y^a is absent or selected from 0, NR^{a^1} , $S(0)_p$, and C(0);

Z^a is selected from H, a C₃₋₁₃ carbocycle substituted with 0-5 R^c and a 5-14 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p and substituted with 0-5 R^c;

provided that Z, U^a , Y^a , and Z^a do not combine to form a N-N, N-O, O-N, O-O, $S(O)_p$ -O, O- $S(O)_p$ or $S(O)_p$ -S(O)_p group;

 R^1 is selected from H, C_{1-4} alkyl, phenyl, and benzyl;

- 15 R^2 is selected from Q, Cl, F, C_{1-10} alkylene-Q substituted with 0-3 R^{b1} , C_{2-10} alkenylene-Q substituted with 0-3 R^{b1} , C_{2-10} alkynylene-Q substituted with 0-3 R^{b1} , $(CR^aR^{a^1})_{r^1}O(CR^aR^{a^1})_{r^2}Q$, $(CR^aR^{a^1})_{r^1}NR^a(CR^aR^{a^1})_{r^2}Q$, $(CR^aR^{a^1})_{r^2}C(0)(CR^aR^{a^1})_{r^2}Q$, $(CR^aR^{a^1})_{r^2}C(0)O(CR^aR^{a^1})_{r^2}Q$,
- $(CR^{a}R^{a^{1}})_{r^{1}}NR^{a}C(0)O(CR^{a}R^{a^{1}})_{r}-Q,$ $(CR^{a}R^{a^{1}})_{r^{1}}NR^{a}C(0)NR^{a}(CR^{a}R^{a^{1}})_{r}-Q, (CR^{a}R^{a^{1}})_{r^{1}}S(0)_{p}(CR^{a}R^{a^{1}})_{r}-Q,$ $(CR^{a}R^{a^{1}})_{r^{1}}SO_{2}NR^{a}(CR^{a}R^{a^{1}})_{r}-Q, (CR^{a}R^{a^{1}})_{r^{1}}NR^{a}SO_{2}(CR^{a}R^{a^{1}})_{r}-Q, \text{ and }$ $(CR^{a}R^{a^{1}})_{r^{1}}NR^{a}SO_{2}NR^{a}(CR^{a}R^{a^{1}})_{r}-Q;$
- 30 R^{2a} is selected from H, C_{1-6} alkyl, OR^a , $NR^aR^{a^1}$, and $S(O)_pR^a$; R^{2b} is H or C_{1-6} alkyl;

Q is selected from H, a C_{3-13} carbocycle substituted with 0-5 R^d and a 5-14 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(0)_p$ and substituted with 0-5 R^d ;

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- 15 Q¹ is selected from H, phenyl substituted with 0-3 R^d,
 naphthyl substituted with 0-3 R^d and a 5-10 membered
 heteroaryl comprising: carbon atoms and 1-4
 heteroatoms selected from the group consisting of N, O,
 and S(O)_p and substituted with 0-3 R^d;
 - R^a , at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl and benzyl;
- R^{a^1} , at each occurrence, is independently selected from H and C_{1-4} alkyl;
 - alternatively, R^a and R^{a^1} when attached to a nitrogen are taken together with the nitrogen to which they are attached to form a 5 or 6 membered ring comprising carbon atoms and from 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(0)_D$;

 R^{a^2} , at each occurrence, is independently selected from C_{1-4} alkyl, phenyl and benzyl;

- Rb, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, I, =O, -CN, NO_2 , $NR^aR^{a^1}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a^1}$, $R^aNC(O)NR^aR^{a^1}$, $OC(O)NR^aR^{a^1}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a^1}$, $NR^aS(O)_2R^a^2$, $NR^aS(O)_2NR^aR^{a^1}$, $OS(O)_2NR^aR^{a^1}$, $OS(O)_2NR^aR^{a^1}$, $OS(O)_2R^aR^a$, $OS(O)_2R^a$, $OS(O)_2R^$
- 10 R^{b1}, at each occurrence, is independently selected from OR^a,
 Cl, F, Br, I, =0, -CN, NO₂, and NR^aR^{a¹};
- R^c, at each occurrence, is independently selected from C₁₋₆
 alkyl, ORa, Cl, F, Br, I, =0, -CN, NO₂, NRaRa, C(0)Ra,

 C(0)ORa, C(0)NRaRa, RaNC(0)NRaRa, OC(0)NRaRa, RaNC(0)O,
 S(0)₂NRaRa, NRaS(0)₂Ra, NRaS(0)₂NRaRa, OS(0)₂NRaRa,
 NRaS(0)₂Ra, S(0)_pRa, CF₃, CF₂CF₃, C₃₋₁₀ carbocycle
 substituted with 0-3 R^{c1} and a 5-14 membered heterocycle
 comprising: carbon atoms and 1-4 heteroatoms selected
 from the group consisting of N, O, and S(0)_p and
 substituted with 0-3 R^{c1};
 - R^{c1} , at each occurrence, is independently selected from C_{T-6} alkyl, OR^a , Cl, F, Br, I, =O, -CN, NO_2 , $NR^aR^{a^1}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a^1}$, $R^aNC(O)NR^aR^{a^1}$, $OC(O)NR^aR^{a^1}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a^1}$, $NR^aS(O)_2R^a$, $NR^aS(O)_2R^a$, $NR^aS(O)_2R^a$, $OS(O)_2NR^aR^a$, $OS(O)_2NR^aR^a$, $OS(O)_2R^a$,

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 R^d , at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, I, =0, -CN, NO_2 , $NR^aR^{a^1}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a^1}$, $R^aNC(O)NR^aR^{a^1}$, $OC(O)NR^aR^{a^1}$, $R^aNC(O)O$, $S(O)_2NR^aR^{a^1}$, $NR^aS(O)_2R^a$, $NR^aS(O)_2NR^aR^{a^1}$, $OS(O)_2NR^aR^{a^1}$,

 $NR^{a}S(0)_{2}R^{a^{2}}$, $S(0)_{p}R^{a^{2}}$, CF_{3} , $CF_{2}CF_{3}$, C_{3-10} carbocycle and a 5-14 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(0)_{p}$;

5.

- $R^5,$ at each occurrence, is selected from C_{1-10} alkyl substituted with 0-2 $R^b,$ and C_{1-8} alkyl substituted with 0-2 $R^e;$
- 10 Re, at each occurrence, is selected from phenyl substituted with 0-2 Rb and biphenyl substituted with 0-2 Rb;
 - R⁶, at each occurrence, is selected from phenyl, naphthyl,

 C₁₋₁₀ alkyl-phenyl-C₁₋₆ alkyl-, C₃₋₁₁ cycloalkyl, C₁₋₆

 alkylcarbonyloxy-C₁₋₂ alkyl-, C₁₋₆ alkoxycarbonyloxy-C₁₋₆
- alkylcarbonyloxy-C₁₋₃ alkyl-, C₁₋₆ alkoxycarbonyloxy-C₁₋₃ alkyl-, C₂₋₁₀ alkoxycarbonyl, C₃₋₆ cycloalkylcarbonyloxy-C₁₋₃ alkyl-, C₃₋₆ cycloalkoxycarbonyloxy-C₁₋₃ alkyl-, C₃₋₆ cycloalkoxycarbonyl, phenoxycarbonyl,
- phenyloxycarbonyloxy- C_{1-3} alkyl-, phenylcarbonyloxy- C_{1-3} alkyl-, C_{1-6} alkoxy- C_{1-6} alkylcarbonyloxy- C_{1-3} alkyl-, $[5-(C_1-C_5 \text{ alkyl})-1,3-\text{dioxa-cyclopenten-2-one-yl}] \text{methyl}, \\ [5-(R^a)-1,3-\text{dioxa-cyclopenten-2-one-yl}] \text{methyl}, \\ (5-\text{aryl-1},3-\text{dioxa-cyclopenten-2-one-yl}) \text{methyl}, -C_{1-10}$ alkyl-NR⁷R^{7a}, -CH(R⁸)OC(=0)R⁹, and -CH(R⁸)OC(=0)OR⁹;
 - R^7 is selected from H and C_{1-10} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl- C_{1-3} alkyl-, and phenyl- C_{1-6} alkyl-;
- 30 R^{7a} is selected from H and C_{1-10} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl- C_{1-3} alkyl-, and phenyl- C_{1-6} alkyl-;
 - R^8 is selected from H and C_{1-4} linear alkyl;

 R^9 is selected from H, C_{1-8} alkyl substituted with 1-2 R^f , C_{3-8} cycloalkyl substituted with 1-2 R^f , and phenyl substituted with 0-2 R^b ;

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- R^f , at each occurrence, is selected from C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{1-5} alkoxy, and phenyl substituted with 0-2 R^b ;
- 10 p, at each occurrence, is selected from 0, 1, and 2;
 - r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and,
- 15 r^1 , at each occurrence, is selected from 0, 1, 2, 3, and 4.
 - 2. A compound according to Claim 1, wherein the compound is of formula II:

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II

- or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;
- 25 A is selected from $-CO_2H$, CH_2CO_2H , -CONHOH, $-CONHOR^5$, $-CONHOR^6$, $-N(OH)COR^5$, -N(OH)CHO, -SH, and $-CH_2SH$;
- ring B is a 4-7 membered non-aromatic carbocyclic or._
 heterocyclic ring comprising: carbon atoms, 0-1
 carbonyl groups, 0-1 double bonds, and from 0-2 ring

heteroatoms selected from O, N, and NR², provided that ring B contains other than a O-O bond;

- Z is absent or selected from a C₃₋₁₁ carbocycle substituted
 with 0-4 R^b and a 5-11 membered heterocycle comprising:
 carbon atoms and 1-4 heteroatoms selected from the
 group consisting of N, O, and S(O)_p and substituted
 with 0-3 R^b;
- 10 U^a is absent or is selected from: 0, NR^{a^1} , C(0), C(0)0, C(0)N R^{a^1} , NR^{a^1} C(0), S(0)p, and S(0)p NR^{a^1} ;
 - X^a is absent or selected from C_{1-4} alkylene, C_{2-4} alkenylene, and C_{2-4} alkynylene;
 - Ya is absent or selected from O and NRa1;

- Z^a is selected from H, a C₃₋₁₀ carbocycle substituted with 0-5 R^c and a 5-10 membered heterocycle comprising:

 carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p and substituted with 0-5 R^c;
- provided that Z, U^a , Y^a , and Z^a do not combine to form a N-N, N-O, O-N, O-O, $S(O)_p$ -O, O- $S(O)_p$ or $S(O)_p$ -S(O)_p group;
 - R^1 is selected from H, C_{1-4} alkyl, phenyl, and benzyl;
- R² is selected from Q, C_{1-6} alkylene-Q, C_{2-6} alkenylene-Q, $C_{2-6} \text{ alkynylene-Q, } (CR^aR^{a^1})_{r^1}O(CR^aR^{a^1})_{r}-Q,$ $(CR^aR^{a^1})_{r^1}NR^a(CR^aR^{a^1})_{r}-Q, (CR^aR^{a^1})_{r^1}C(O)(CR^aR^{a^1})_{r}-Q,$ $(CR^aR^{a^1})_{r^1}C(O)O(CR^aR^{a^1})_{r}-Q, (CR^aR^{a^1})_{r}C(O)NR^aR^{a^1},$

WO 01/70673 PCT/US01/08334 $(CR^{a}R^{a^{1}})_{r^{1}}C(0)NR^{a}(CR^{a}R^{a^{1}})_{r}-Q, (CR^{a}R^{a^{1}})_{r^{1}}S(0)_{p}(CR^{a}R^{a^{1}})_{r}-Q,$ and $(CR^{a}R^{a^{1}})_{r^{1}}SO_{2}NR^{a}(CR^{a}R^{a^{1}})_{r}-Q;$

- Q is selected from H, a C₃₋₆ carbocycle substituted with 0-5

 R^d, and a -5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p and substituted with 0-5

 R^d;
- 10 Ra, at each occurrence, is independently selected from H, C₁₋₄ alkyl, phenyl and benzyl;

- R^{a^1} , at each occurrence, is independently selected from H and C_{1-4} alkyl;
- alternatively, R^a and R^{a¹} when attached to a nitrogen are taken together with the nitrogen to which they are attached to form a 5 or 6 membered ring comprising carbon atoms and from 0-1 additional heteroatoms selected from the group consisting of N, O, and S(O)_p;
 - R^{a^2} , at each occurrence, is independently selected from C_{1-4} alkyl, phenyl and benzyl;
- 25 R^b , at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, =O, -CN, $NR^aR^{a^1}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a^1}$, $S(O)_2NR^aR^{a^1}$, $S(O)_pR^{a^2}$, and CF_3 ;
- R^c , at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, =0, -CN, $NR^aR^{a^1}$, $C(0)R^a$, $C(0)OR^a$, $C(0)NR^aR^{a^1}$, $S(0)_2NR^aR^{a^1}$, $S(0)_pR^{a^2}$, CF_3 , C_{3-6} carbocycle and a 5-6 membered heterocycle comprising: carbon

atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)p;

Rd, at each occurrence, is independently selected from C₁₋₆

alkyl, ORa, Cl, F, Br, =0, -CN, NRaRa, C(0)Ra, C(0)ORa,
C(0)NRaRa, S(0)2NRaRa, S(0)pRa, CF3, C3-6 carbocycle
and a 5-6 membered heterocycle comprising: carbon
atoms and 1-4 heteroatoms selected from the group
consisting of N, O, and S(0)p;

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- $R^5,$ at each occurrence, is selected from C_{1-6} alkyl substituted with 0-2 $R^b,$ and C_{1-4} alkyl substituted with 0-2 $R^e;$
- 15 R^e , at each occurrence, is selected from phenyl substituted with 0-2 R^b and biphenyl substituted with 0-2 R^b ;
- R⁶, at each occurrence, is selected from phenyl, naphthyl,

 C₁₋₁₀ alkyl-phenyl-C₁₋₆ alkyl-, C₃₋₁₁ cycloalkyl, C₁₋₆

 20 alkylcarbonyloxy-C₁₋₃ alkyl-, C₁₋₆ alkoxycarbonyloxy-C₁₋₃

 alkyl-, C₂₋₁₀ alkoxycarbonyl, C₃₋₆

 cycloalkylcarbonyloxy-C₁₋₃ alkyl-, C₃₋₆

 cycloalkoxycarbonyloxy-C₁₋₃ alkyl-, C₃₋₆

 cycloalkoxycarbonyl, phenoxycarbonyl,

 phenyloxycarbonyloxy-C₁₋₃ alkyl-, phenylcarbonyloxy-C₁₋₃

 alkyl-, C₁₋₆ alkoxy-C₁₋₆ alkylcarbonyloxy-C₁₋₃ alkyl-,

 [5-(C₁-C₅ alkyl)-1,3-dioxa-cyclopenten-2-one-yl]methyl,

 [5-(R^a)-1,3-dioxa-cyclopenten-2-one-yl]methyl,

 (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyl, -C₁₋₁₀
 - \mbox{R}^{7} is selected from H and \mbox{C}_{1-6} alkyl, \mbox{C}_{2-6} alkenyl, \mbox{C}_{3-6}

cycloalkyl-C₁₋₃ alkyl-, and phenyl-C₁₋₆ alkyl-;

alkyl-NR⁷R^{7a}, -CH(R⁸)OC(=0)R⁹, and -CH(R⁸)OC(=0)OR⁹;

 R^{7a} is selected from H and C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl- C_{1-3} alkyl-, and phenyl- C_{1-6} alkyl-;

5 \mathbb{R}^8 is selected from H and \mathbb{C}_{1-4} linear alkyl;

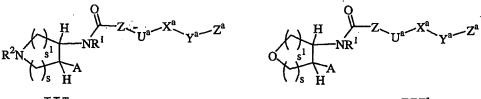
Rb;

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 R^9 is selected from H, C_{1-6} alkyl substituted with 1-2 R^f , C_{3-6} cycloalkyl substituted with 1-2 R^f , and phenyl substituted with 0-2 R^b ;

10 $R^{\rm f}, \mbox{ at each occurrence, is selected from C_{1-4} alkyl, C_{3-6} \\ cycloalkyl, C_{1-5} alkoxy, and phenyl substituted with $0-2$ }$

- 15 p, at each occurrence, is selected from 0, 1, and 2;
 - r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and,
- 20 r1, at each occurrence, is selected from 0, 1, 2, 3, and 4.
 - 3. A compound according to Claim 2, wherein the compound is of formula IIIa or IIIb:



IIIa IIIb

- or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;
- 30 A is selected from $-CO_2H$, CH_2CO_2H , -CONHOH, $-CONHOR^5$, -N(OH)CHO, and $-N(OH)COR^5$;

Z is absent or selected from a C₅₋₆ carbocycle substituted with 0-3 R^b and a 5-6 membered heteroaryl comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p and substituted with 0-3 R^b;

 U^a is absent or is selected from: O, NR^{a^1} , C(O), C(O) NR^{a^1} , S(O)_p, and S(O)_p NR^{a^1} ;

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 X^a is absent or selected from C_{1-4} alkylene, C_{2-4} alkenylene, and C_{2-4} alkynylene

Ya is absent or selected from O and NRa1;

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 Z^a is selected from H, a C_{5-6} carbocycle substituted with 0-3 R^c and a 5-10 membered heteroaryl comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(0)_p$ and substituted with 0-3

20 Rc;

- provided that Z, U^a , Y^a , and Z^a do not combine to form a N-N, N-O, O-N, O-O, $S(O)_p$ -O, O- $S(O)_p$ or $S(O)_p$ - $S(O)_p$ group;
- 25 R^1 is selected from H, C_{1-4} alkyl, phenyl, and benzyl;
 - R² is selected from Q, C_{1-6} alkylene-Q, C_{2-6} alkenylene-Q, C_{2-6} alkynylene-Q, $(CR^aR^{a^1})_{r^1}C(0)(CR^aR^{a^1})_{r^-}Q$, $(CR^aR^{a^1})_{r^1}C(0)O(CR^aR^{a^1})_{r^-}Q$, $(CR^aR^{a^2})_{r^1}C(0)NR^aR^{a^1}$, $(CR^aR^{a^2})_{r^1}C(0)NR^a(CR^aR^{a^1})_{r^-}Q$, and $(CR^aR^{a^1})_{r^1}S(0)_{r^1}(CR^aR^{a^1})_{r^-}Q$;

Q is selected from H, $_{-a}$ C $_{3-6}$ carbocycle substituted with 0-3 R^d and a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p and substituted with 0-3 R^d;

- R^a , at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl and benzyl;
- 10 R^{a1} , at each occurrence, is independently selected from H and C_{1-4} alkyl;
 - R^{a^2} , at each occurrence, is independently selected from C_{1-4} alkyl, phenyl, and benzyl;

- R^b , at each occurrence, is independently selected from C_{1-4} alkyl, OR^a , $Cl_{E/F}$; =0, $NR^aR^{a^1}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a^1}$, $S(O)_2NR^aR^{a^1}$, $S(O)_pR^{a^2}$, and CF_3 ;
- 20 R^c , at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, =0, $NR^aR^{a^1}$, $C(0)R^a$, $C(0)NR^aR^{a^1}$, $S(0)_2NR^aR^{a^1}$, $S(0)_DR^{a^2}$, and CF_3 ;
- R^d , at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, =0, $NR^aR^{a^1}$, $C(O)R^a$, $C(O)NR^aR^{a^1}$, $S(O)_2NR^aR^{a^1}$, $S(O)_pR^{a^2}$, CF_3 , and phenyl;
- R^5 , at each occurrence, is selected from C_{1-4} alkyl substituted with 0-2 R^b , and C_{1-4} alkyl substituted with 0-2 R^e ;
 - R^e , at each occurrence, is selected from phenyl substituted with 0-2 R^b and biphenyl substituted with 0-2 R^b ;

- p, at each occurrence, is selected from 0, 1, and 2;
- r, at each occurrence, is selected from 0, 1, 2, 3, and 4;
- r¹, at each occurrence, is selected from 0, 1, 2, 3, and 4; and,
- s and s¹ combine to total 2, 3, or 4.

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4. A compound according to Claim 3, wherein the compound is of formula IVa or IVb:

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- or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;
- Z is absent or selected from phenyl substituted with 0-3 R^b
 and pyridyl substituted with 0-3 R^b;
 - Ua is absent or is 0;
 - Xa is absent or is CH2 or CH2CH2;

- Ya is absent or is 0;
- Za is selected from H, phenyl substituted with 0-3 Rc, pyridyl substituted with 0-3 Rc, and quinolinyl substituted with 0-3 Rc;

provided that Z, U^a , Y^a , and Z^a do not combine to form a N-N, N-O, O-N, or O-O group;

R¹ is selected from H, CH₃, and CH₂CH₃;

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- R² is selected from Q, C_{1-6} alkylene-Q, C_{2-6} alkynylene-Q, $C(0) (CR^aR^a^i)_{r} = Q_r \wedge C(0) O(CR^aR^a^i)_{r} Q, C(0) NR^a (CR^aR^a^i)_{r} Q, and \\ S(0)_p (CR^aR^a^i)_{r} Q;$
- 10 Q is selected from H, cyclopropyl substituted with 0-1 R^d, cyclobutyl substituted with 0-1 R^d, cyclopentyl substituted with 0-1 R^d, cyclohexyl substituted with 0-1 R^d, phenyl substituted with 0-2 R^d and a heteroaryl substituted with 0-3 R^d, wherein the heteroaryl is selected from pyridyl, quinolinyl, thiazolyl, furanyl, imidazolyl, and isoxazolyl;
 - R^a , at each occurrence, is independently selected from H, CH_3 , and CH_2CH_3 ;

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- R^{a^1} , at each occurrence, is independently selected from H, CH_3 , and CH_2CH_3 ;
- Ra², at each occurrence, is independently selected from H,
 CH₃, and CH₂CH₃;
 - R^b , at each occurrence, is independently selected from C_{1-4} alkyl, OR^a , Cl, F, =0, $NR^aR^{a^1}$, $C(0)R^a$, $C(0)OR^a$, $C(0)NR^aR^{a^1}$, $S(0)_2NR^aR^{a^1}$, $S(0)_DR^{a^2}$, and CF_3 ;

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 R^{C} , at each occurrence, is independently selected from C_{1-6} alkyl, OR^{a} , Cl, F, Br, =O, $NR^{a}R^{a^{1}}$, $C(O)R^{a}$, $C(O)NR^{a}R^{a^{1}}$, $S(O)_{D}R^{a}R^{a^{2}}$, and CF_{3} ;

 R^d , at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, =0, $NR^aR^a^1$, $C(0)R^a$, $C(0)NR^aR^{a^1}$, $S(0)_2NR^aR^{a^1}$, $S(0)_pR^{a^2}$, CF_3 and phenyl;

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- p, at each occurrence, is selected from 0, 1, and 2;
- r, at each occurrence, is selected from 0, 1, 2, and 3;
- 10 r^1 , at each occurrence, is selected from 0, 1, 2, and 3; and, s and s^1 combine to total 2, 3, or 4.
- 15 5. A compound according to Claim 2, wherein;
 - A is selected from -CO₂H, CH₂CO₂H, -CONHOH, -CONHOR⁵, -N(OH)CHO, and -N(OH)COR⁵;
- ring B is a 4-7 membered non-aromatic carbocyclic or heterocyclic ring comprising: carbon atoms, 0-1 carbonyl groups, 0-1 double bonds, and from 0-2 ring heteroatoms selected from 0, N, and NR², provided that ring B contains other than a 0-0 bond;

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- Z is absent or selected from a C_{5-6} carbocycle substituted with 0-3 R^b and a 5-6 membered heteroaryl comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(0)_p$ and substituted with 0-3 R^b ;
- Ua is absent or is selected from: O, NRa1, C(O), C(O)NRa1,

 $S(0)_p$, and $S(0)_pNR^{a^1}$;

 X^a is absent or selected from C_{1-2} alkylene, C_{2-4} alkenylene, and C_{2-4} alkynylene

Ya is absent or selected from O and NRa1;

5

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- Z^a is selected from H, a C_{5-6} carbocycle substituted with 0-3 R^c and a 5-10 membered heteroaryl comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(0)_p$ and substituted with 0-3 R^c ;
- provided that Z, U^a , Y^a , and Z^a do not combine to form a N-N, N-O, O-N, O-O, $S(O)_p$ -O, O- $S(O)_p$ or $S(O)_p$ -S(O)_p group;
- 15 R^1 is selected from H, C_{1-4} alkyl, phenyl, and benzyl;
 - R^2 is $(CR^aR^{a^1})_{r^1}O(CR^aR^{a^1})_{r^2}Q$ or $(CR^aR^{a^1})_{r^1}NR^a(CR^aR^{a^1})_{r^2}Q$;
- Q is selected from H, a C₃₋₆ carbocycle substituted with 0-3

 R^d and a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p and substituted with 0-3

 R^d;
- 25 R^a , at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl and benzyl;
 - R^{a^1} , at each occurrence, is independently selected from H and C_{1-4} alkyl;

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 R^{a^2} , at each occurrence, is independently selected from C_{1-4} alkyl, phenyl and benzyl;

 R^b , at each occurrence, is independently selected from C_{1-4} alkyl, OR^a , C1, F, =0, $NR^aR^{a^1}$, $C(0)R^a$, $C(0)OR^a$, $C(0)NR^aR^{a^1}$, $S(0)_2NR^aR^{a^1}$, $S(0)_pR^{a^2}$, and CF_3 ;

- 5 R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, =0, $NR^aR^{a^1}$, $C(O)R^a$, $C(O)NR^aR^{a^1}$, $S(O)_2NR^aR^{a^1}$, $S(O)_pR^{a^2}$, and CF_3 ;
- R^d , at each occurrence, is independently selected from C_{1-6} alkyl, OR^a , Cl, F, Br, =O, $NR^aR^{a^1}$, $C(O)R^a$, $C(O)NR^aR^{a^1}$, $S(O)_DR^aR^{a^2}$, CF_3 and phenyl;
- R^5 , at each occurrence, is selected from C_{1-4} alkyl substituted with 0-2 R^b , and C_{1-4} alkyl substituted with 15 0-2 R^e ;
 - R^e, at each occurrence, is selected from phenyl substituted with 0-2 R^b and biphenyl substituted with 0-2 R^b;
- 20 p, at each occurrence, is selected from 0, 1, and 2;
 - r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and,
- 25 r¹, at each occurrence, is selected from 0, 1, 2, 3, and 4.
 - 6. A compound according to Claim 5, wherein;
- 30 A is -CONHOH;
 - ring B is a 5-6 membered non-aromatic carbocyclic or heterocyclic ring comprising: carbon atoms, 0-1 carbonyl groups, 0-1 double bonds, and from 0-2 ring

heteroatoms selected from O, N, and NR², provided that ring B contains other than a O-O bond;

Z is absent or selected from phenyl substituted with 0-3 R^b and pyridyl substituted with 0-3 R^b;

Ua is absent or is 0;

Xa is absent or is CH2 or CH2CH2;

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Ya is absent or is 0;

Za is selected from H, phenyl substituted with 0-3 Rc,
pyridyl substituted with 0-3 Rc, and quinolinyl
substituted with 0-3 Rc;

provided that Z, U^a, Y^a, and Z^a do not combine to form a N-N, N-O, O-N, or O-O group;

20 R¹ is selected from H, CH₃, and CH₂CH₃;

 R^2 is $(CR^aR^{a^1})_{r^1}O(CR^aR^{a^1})_{r^2}Q$ or $(CR^aR^{a^1})_{r^1}NR^a(CR^aR^{a^1})_{r^2}Q$;

- Q is selected from H, cyclopropyl substituted with 0-1 R^d,

 cyclobutyl substituted with 0-1 R^d, cyclopentyl
 substituted with 0-1 R^d, cyclohexyl substituted with

 0-1 R^d, phenyl substituted with 0-2 R^d, and a heteroaryl
 substituted with 0-3 R^d, wherein the heteroaryl is
 selected from pyridyl, quinolinyl, thiazolyl, furanyl,

 imidazolyl, and isoxazolyl;
 - R^a , at each occurrence, is independently selected from H, CH_3 , and CH_2CH_3 ;

Ra1, at each occurrence, is independently selected from H, CH3, and CH2CH3;

- Ra², at each occurrence, is independently selected from H,
 CH₃, and CH₂CH₃;
 - R^b , at each occurrence, is independently selected from C_{1-4} alkyl, OR^a , Cl, F, =0, $NR^aR^{a^1}$, $C(0)R^a$, $C(0)OR^a$, $C(0)NR^aR^{a^1}$, $S(0)_2NR^aR^{a^1}$, $S(0)_pR^{a^2}$, and CF_3 ;

 R^{c} , at each occurrence, is independently selected from C_{1-6} alkyl, OR^{a} , Cl, F, Br, =0, $NR^{a}R^{a^{1}}$, $C(0)R^{a}$, $C(0)NR^{a}R^{a^{1}}$, $S(0)_{2}NR^{a}R^{a^{1}}$, $S(0)_{n}R^{a^{2}}$, and CF_{3} ;

- 15 R^d, at each occurrence, is independently selected from C₁₋₆ alkyl, OR^a, Cl, F, Br, =0, NR^aR^{a¹}, C(0)R^a, C(0)NR^aR^{a¹}, S(0)₂NR^aR^{a¹}, S(0)_pR^{a²}, CF₃ and phenyl;
- p, at each occurrence, is selected from 0, 1, and 2;
 - r, at each occurrence, is selected from 0, 1, 2, and 3; and,
 - r^{1} , at each occurrence, is selected from 0, 1, 2, and 3.

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- 7. A compound according to Claim 1, wherein the compound is selected from the group:
- N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-2'-30 (trifluoromethyl)[1,1'-biphenyl]-4-carboxamide
 - N-{ (1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-4-[2-(trifluoromethyl)phenoxy]benzamide
- 35 N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-4-(3-methyl-2-pyridinyl)benzamide

 $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}[1,1'$ biphenyl]-4-carboxamide $N-\{(1R, 2S)-2-[(hydroxyamino) carbonyl] cyclopentyl\}-4-$ 5 phenoxybenzamide $4-(benzyloxy)-N-\{(1R,2S)-2-$ [(hydroxyamino)carbonyl]cyclopentyl}benzamide 10 $N-\{(1R, 2S)-2-[(hydroxyamino) carbonyl] cyclopentyl\}-2'$ methoxy[1,1'-biphenyl]-4-carboxamide $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-2'$ methyl[1,1'-biphenyl]-4-carboxamide 15 $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-4-(2$ methoxyphenoxy) benzamide $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-4-(2-$ 20 methylphenoxy) benzamide $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-4-(3$ methylphenoxy) benzamide 25 $4-(5, 8-dihydro-4-quinolinyl) -N-{(1R, 2S)-2-}$ [(hydroxyamino)carbonyl]cyclopentyl}benzamide $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-3',5'$ dimethyl[1,1'-biphenyl]-4-carboxamide 30 $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-6-(2$ methylphenyl)nicotinamide

- $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl\}-6-(2-35 methoxyphenyl)nicotinamide$
 - (3S, 4S) -N-hydroxy-1-isopropyl-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
 - (3S,4S)-1-(2,2-dimethylpropanoyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
- 45 (3S,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-(methylsulfonyl)-3-pyrrolidinecarboxamide
- (3S, 4S) -N-hydroxy-1-methyl-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide

tert-butyl (3S, 4S)-3-[(hydroxyamino)carbonyl]-4-($\{4-[(2$ methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate 5 quinolinyl)methoxy]benzoyl}amino)-3pyrrolidinecarboxamide tert-butyl 4-[cis-3-[(hydroxyamino)carbonyl]-4-({4-[(2-10 methvl-4quinolinyl)methoxy]benzoyl}amino)pyrrolidinyl]-1piperidinecarboxylate $cis-N-hydroxy-4-({4-[(2-methyl-4-$ 15 quinolinyl)methoxy]benzoyl}amino)-1-(4-piperidinyl)-3pyrrolidinecarboxamide cis-1-[3-[(1,1-dimethylethoxy)carbonyl]pyrollidinyl]-Nhydroxy-3-[[[4-[(2-methyl-4-20 quinolinyl)methoxy]phenyl]carbonyl]amino]-4pyrollidinecarboxamide cis-N-hydroxy-1-[3-pyrollidinyl]-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-4-25 pyrollidinecarboxamide tert-butyl (3R, 4R)-3-[(hydroxyamino)carbonyl]-4-({4-[(2methyl-4-quinolinyl)methoxy|benzoyl}amino)-1pyrrolidinecarboxylate 30 tert-butyl (3S, 4R)-3-[(hydroxyamino)carbonyl]-4-({4-[(2methyl-4-quinolinyl)methoxy|benzoyl}amino)-1pyrrolidinecarboxylate 35 $(3S, 4R) - N - hydroxy - 4 - (\{4 - [(2 - methy] - (\{4 - [(2 - methy] - 4 - ([2 - methy] - (\{4 - [(2 - methy] - 4 - ([2 - methy] - (\{4 - [(2 - m$ quinolinyl)methoxy]benzoyl}amino)-3pyrrolidinecarboxamide . tert-butyl (3R, 4S)-3-[(hydroxyamino)carbonyl]-4-($\{4$ -[(2-40 methyl-4-quinolinyl)methoxy|benzoyl}amino)-1pyrrolidinecarboxylate $(3R, 4S) - N - hydroxy - 4 - (\{4 - [(2 - methy] - 4 - (\{4 - [(4 - [(2 - methy] - 4 - (\{4 - [($ quinolinyl)methoxy]benzoyl}amino)-3-45 pyrrolidinecarboxamide N-{(1R,2S)-2-[(hydroxyamino)carbonyl]cyclopentyl}-4-(4pyridinyl) benzamide 50 $(3S, 4S) - 1 - (1, 1 - dimethyl - 2 - propynyl) - N - hydroxy - 4 - ({4 - [(2 - quarter)left - 2 - propynyl)] - N - hydrox$ methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-

pyrrolidinecarboxamide

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quinolinyl)methoxy]benzoyl}amino)-1-(2-propynyl)-3-
                                                                                               pyrrolidinecarboxamide
            5
                                                 quinolinyl)methoxy|benzoyl}amino)-3-
                                                                                               pyrrolidinecarboxamide
  10
                                                (3S, 4S) - N - hydroxy - 4 - (\{4 - \{(2 - methyl - 4 - (\{4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 - \{(4 + \{(4 - \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + \{(4 + ((4 + \{(4 + ((4 + ((4 + ((4 + ((4) + ((4 + ((4 + ((4)))))))))}))})})})})})})})})})})
                                                                                                 quinolinyl)methoxy|benzoyl}amino)-1-propyl-3-
                                                                                               pyrrolidinecarboxamide
                                                 (3S, 4S) - N - hydroxy - 1 - (2 - methyl - 2 - propenyl) - 4 - (\{4 - [(2 - methyl - 3)] - 1 - (3)] - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) - (3) -
  15
                                                                                                 4-quinolinyl)methoxy]benzoyl}amino)-3-
                                                                                               pyrrolidinecarboxamide
                                                 (3S, 4S) - 1 - (1, 1 - dimethyl - 2 - propenyl) - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - [(2 - 1) - 2 - propenyl)]} - N - hydroxy - 4 - ({4 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 - [(2 -
                                                                                              methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-
  20
                                                                                               pyrrolidinecarboxamide
                                                 quinolinyl)methoxy]benzoyl}amino)-1-tert-pentyl-3-
                                                                                               pyrrolidinecarboxamide
 25 -
                                                quinolinyl)methoxy]benzoyl}amino)-3-
                                                                                 pyrrolidinecarboxamide
  30
                                                (3S, 4S) - N - hydroxy - 4 - (\{4 - [(2 - methy 1 - 4 - [(3 - met
                                                                                               quinolinyl)methoxy]benzoyl}amino)-1-neopentyl-3-
                                                                                               pyrrolidinecarboxamide
                                                 (3S, 4S) - 1 - \text{butyl} - N - \text{hydroxy} - 4 - (\{4 - [(2 - \text{methyl} - 4 - ((3 - \text{methyl}) - ((3 - \text{methyl}) - 4 - ((3 - \text{methyl}) - ((3 - \text{m
 35
                                                                                               quinolinyl)methoxy]benzoyl}amino)-3-
                                                                                              pyrrolidinecarboxamide
                                                (3S, 4S) - 1 - (3-butenyl) - N-hydroxy - 4 - ({4-[(2-methyl) - 4-(3-butenyl)]} - N-hydroxy - ({4-[(2-methyl) - 4-(3-(2-butenyl)]} - N-hydroxy - ({4-[(2-methyl) - 4-(2-(2-bu
                                                                                               quinolinyl)methoxy]benzoyl}amino)-3-
 40
                                                                                             pyrrolidinecarboxamide
                                               quinolinyl)methoxy]benzoyl}amino)-3-
                                                                                             pyrrolidinecarboxamide
 45
                                               (3S, 4S) - 1 - (2 - \text{furylmethyl}) - N - \text{hydroxy} - 4 - (\{4 - [(2 - \text{methyl}) - 4 - ((3S - 4S))]))]
                                                                                              quinolinyl)methoxy|benzoyl}amino)-3-
                                                                                             pyrrolidinecarboxamide
50
                                               (3S, 4S) - N - hydroxy - 1 - [(5 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl] - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 - furyl) methyl - 4 - ({4 - [(2 - methyl - 2 
                                                                                             methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-
                                                                                             pyrrolidinecarboxamide
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5	<pre>(3R,4S)-N-hydroxy-4-({4-[(2-methyl-4- quinolinyl)methoxy}benzoyl}amino)tetrahydro-3- furancarboxamide</pre>
	<pre>(3S,4R)-N-hydroxy-4-({4-[(2-methyl-4- quinolinyl)methoxy]benzoyl}amino)tetrahydro-3- furancarboxamide</pre>
10	(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-(1,3-thiazol-2-ylmethyl)-3-pyrrolidinecarboxamide
15	<pre>(3S,4S)-1-acetyl-N-hydroxy-4-({4-[(2-methyl-4- quinolinyl)methoxy]benzoyl}amino)-3- pyrrolidinecarboxamide</pre>
2Ó	<pre>(3S,4S)-N-hydroxy-1-isobutyryl-4-({4-[(2-methyl-4- quinolinyl)methoxy]benzoyl}amino)-3- pyrrolidinecarboxamide</pre>
25	<pre>(3S,4S)-N-hydroxy-1-(3-methylbutanoyl)-4-({4-[(2-methyl-4- quinolinyl)methoxy]benzoyl}amino)-3- pyrrolidinecarboxamide</pre>
2 5	(3S,4S)-1-(cyclopropylcarbonyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
30	(3S,4S)-1-(cyclobutylcarbonyl)-N-hydroxy-4-({4-[(2-methyl-4 quinolinyl)methoxy]benzoyl}amino)-3- pyrrolidinecarboxamide
35	(3S,4S)-N-hydroxy-1-(methoxyacetyl)-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
40	(3S,4S)-1-(2-furoyl)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-3-pyrrolidinecarboxamide
4.5	(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-(2-thienylcarbonyl)-3-pyrrolidinecarboxamide
45	(3S,4S)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-propionyl-3-pyrrolidinecarboxamide
50	(3R,4S)-4-{[4-(2-butynyloxy)benzoyl]amino}-N-hydroxy-

 $N-\{(1R,2S)-2-[(hydroxyamino)carbonyl]-4-oxocyclopentyl\}-4-$ [(2-methyl-4-quinolinyl)methoxy]benzamide $N-\{(1R, 2S, 4R) - 4 - hydroxy - 2 - 4 - hydrox$ 5 [(hydroxyamino)carbonyl]cyclopentyl}-4-[(2-methyl-4quinolinyl) methoxylbenzamide $N-\{(1R, 2S, 4S) - 4 - hydroxy - 2 - 1\}$ [(hydroxyamino)carbonyl]cyclopentyl}-4-[(2-methyl-4-10 quinolinyl)methoxy]benzamide quinolinyl)methoxy]benzoyl}amino)-1-tetrahydro-2Hpyran-4-yl-3-pyrrolidinecarboxamide 15 methyl (3S, 4S) -3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate 20 ethyl $(3S, 4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4$ quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate propyl (3S, 4S) - 3 - [(hydroxyamino) carbonyl] - 4 - ((4 - [(2 - methyl - methyl25 4-quinoliny1)methoxy]benzoy1}amino)-1pyrrolidinecarboxylate allyl $(3S, 4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2-methyl-4$ quinolinyl)methoxy]benzoyl}amino)-1-30 pyrrolidinecarboxylate isopropyl $(3S, 4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2$ methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate 35 2-propyny1 (3S, 4S) $-3-[(hydroxyamino)carbony1] <math>-4-(\{4-[(2-int)max], 4-[(3-int)max], 4-[(3-int)max], 4-[(3-int)max])$ methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate 40 2-butynyl (3S,4S)-3-[(hydroxyamino)carbonyl]-4-({4-[(2methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate 3-butenyl (3S, 4S) -3-[(hydroxyamino)carbonyl]-4-({4-[(2-45 methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate benzyl $(3S, 4S) - 3 - [(hydroxyamino) carbonyl] - 4 - ({4 - [(2-methyl-$ 4-quinolinyl)methoxy|benzoyl}amino)-1-50 pyrrolidinecarboxylate

WO 01/70673 PCT/US01/08334 $N-\{(1R,2S)-4-(dimethylamino)-2-$ [(hydroxyamino)carbonyl]cyclopentyl}-4-[(2-methyl-4quinolinyl) methoxy] benzamide 5 (3S, 4S) -4-{[4-(2-butynyloxy)benzoyl]amino}-N-hydroxy-1isopropyl-3-pyrrolidinecarboxamide N-{(1R,2S)-4,4-difluoro-2-[(hydroxyamino)carbonyl]cyclopentyl}-4-[(2-methyl-4-10 quinolinyl) methoxy] benzamide $(3S, 4S) - N - hydroxy - 1 - isopropyl - 4 - \{ [4 - (2 - 1)] - (3S - 1) - (2 - 1) - (3S - 1) - (3$ methylphenoxy) benzoyl] amino}-3-pyrrolidinecarboxamide 15 cis-N-hydroxy-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-1cyclopentanecarboxamide trans-N-hydroxy-2-[[[4-[(2-methyl-4-20 quinolinyl)methoxy]phenyl]carbonyl]amino]-1cyclopentanecarboxamide (1S, 2R) - N - hydroxy - 2 - [[[4 - [(2 - methy] - 4 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-25 cyclopentanecarboxamide (1R, 2S) - N - hydroxy - 2 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy]phenyl]carbonyl]amino]-1cyclopentanecarboxamide 30 cis-N-hydroxy-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-1cyclohexanecarboxamide 35 trans-N-hydroxy-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-1cyclohexanecarboxamide trans-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-3-[[[4-40 [(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-pyrrolidinecarboxamide trans-N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-4-45 pyrrolidinecarboxamide cis-1-[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-3-[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-pyrrolidinecarboxamide

	<pre>cis-N-hydroxy-3-[[[4-[(2-methyl-4-</pre>
5	(3S,4R)-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-4- [[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-3- piperidinecarboxamide
10	(3S,4S)-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-4- [[[4-[(2-methyl-4- quinolinyl)methoxy]phenyl]carbonyl]amino]-3- piperidinecarboxamide
15	(3S,4S)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
20	(3S,4R)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
25	(3S,4R)-1-[(butoxy)carbonyl]-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
30	(3S,4R)-N-hydroxy-1-[[(1-methylethyl)oxy]carbonyl]-4-[[[4- [(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino] 3-piperidinecarboxamide
	(3S, 4R) -N-hydroxy-1-(methylsulfonyl)-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
35	(3S, 4R) -N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(phenylsulfonyl)-3-piperidinecarboxamide
40	(3S,4R)-1-acetyl-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
45	(3S, 4R)-1-benzoyl-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
E 0	(3S, 4R)-1-(2, 2-dimethylpripionyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
50	

(3S,4R)-1-(3,3-dimethylbutanoyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide

- 5 (3S,4R)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(4-morpholinecarbonyl)-3-piperidinecarboxamide
- (3S, 4R)-1-(dimethylcarbamyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
- (3S, 4R)-N-hydroxy-1-methyl-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
 - (3S, 4R)-1-ethyl-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide

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- (3S, 4R)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-propyl-3-piperidinecarboxamide
- 25 (3S, 4R) -N-hydroxy-1-(1-methylethyl)-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
- (3S, 4R)-1-(cyclopropylmethyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
- (3S, 4R)-1-(2,2-dimethylpropyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
 - (3S, 4R) -1-benzyl-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
 - (3S, 4R)-1-(2-thiazolylmethyl)-N-hydroxy-4-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-3-piperidinecarboxamide
- 45 (3S,4S)-1-[((1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide
- 50 (3R, 4S)-1-[[(1,1-dimethylethyl)oxy]carbonyl]-N-hydroxy-3-[[[4-[(2-methyl-4-

quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide

- (3R,4S)-N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide
- (3S, 4S) -N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide

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- (3S,4S)-N-hydroxy-1-[[(2-methylpropyl)oxy]carbonyl]-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
- (3S, 4S) -N-hydroxy-1-(methoxycarbonyl)-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
- 20 (3S,4S)-N-hydroxy-1-[(1-methylethoxy)carbonyl]-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
- (3S, 4S) -N-hydroxy-1-(methylsulfonyl) -3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
 - (3S, 4S) -N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(phenylsulfonyl)-4-piperidinecarboxamide
 - (3S, 4S)-1-(3,3-dimethylbutanoyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
 - (3S, 4S)-1-(2,2-dimethylpropionyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
- 40 (3S, 4S)-1-benzoyl-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
- (3S,4S)-1-[(pyridin-3-yl)carbonyl]-N-hydroxy-3-[[[4-[(2-45 methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
- (3S, 4S) -N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(2-thiophenecarbonyl)-4-piperidinecarboxamide

WO 01/70673 PCT/US01/08334 (3S, 4S) - 1 - (dimethylcarbamyl) - N - hydroxy - 3 - [[4 - [4 - [4 - [4 - [4]]]]] - N - hydroxy - 3 - [4 - [4 - [4]]]]quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 -5 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(4morpholinecarbonyl)-4-piperidinecarboxamide (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 - 6)]]]]10 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-[[2-(2thienyl)ethyl]carbamyl]-4-piperidinecarboxamide [(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-15 4-piperidinecarboxamide (3S, 4S) - N - hydroxy - 1 - methyl - 3 - [[[4 - [(2 - methyl - 4 - [(3S - 4S) - N - hydroxy - 1 - methyl - 3 - [([4 - [(2 - methyl - 4 - [(3S - 4S) - N - hydroxy - 1 - methyl - 3 - [([4 - [(2 - methyl - 4 - [(3S - 4S) - N - hydroxy - 1 - methyl - 3 - [([4 - [(2 - methyl - 4 - [(3S - 4S) - N - hydroxy - 1 - methyl - 3 - [([4 - [(2 - methyl - 4 - [(3S - 4S) - N - hydroxy - 1 - methyl - 3 - [([4 - [(2 - methyl - 4 - [(3S - 4S) - N - hydroxy - 1 - methyl - 3 - [([4 - [(2 - methyl - 4 - [(3S - 4S) - N - hydroxy - 1 - methyl - 3 - [([4 - [(2 - methyl - 4 - [(3S - 4S) - ((3S - 4S) - ((3Squinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide 20 (3S, 4S) - 1 - ethyl - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 - (2 - methyl) - 4 - (2 - methyl)]]]quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 -25 quinolinyl)methoxylphenyl]carbonyl]amino]-1-propyl-4piperidinecarboxamide (3S, 4S) - N - hydroxy - 1 - (1 - methylethyl) - 3 - [[[4 - [(2 - methyl - 4 - methylethyl)]]]]30 quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide (3S, 4S)-1-cyclobutyl-N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-4-35 piperidinecarboxamide (3S, 4S) - 1 - butyl - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 - ...])]]]quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide 40 (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 - 1)]]]]quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(2methylpropyl)-4-piperidinecarboxamide (3S.4S)-1-(cyclopropylmethyl)-N-hydroxy-3-[[[4-[(2-methyl-4-interval of the context of the con45 quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide (3S, 4S) - 1 - (2, 2 - dimethylpropyl) - N - hydroxy - 3 - [[[4 - [(2 - methyl - methyl - methylpropyl)]]]]50 4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-

piperidinecarboxamide

WO 01/70673 PCT/US01/08334 (3S, 4S)-1-cyclopentyl-N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy[phenyl]carbonyl]amino]-4piperidinecarboxamide (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(4tetrahydropyranyl)-4-piperidinecarboxamide (3S, 4S) - 1 - benzyl - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy[phenyl]carbonyl]amino]-4piperidinecarboxamide (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(2thiazolylmethyl)-4-piperidinecarboxamide (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 quinolinyl) methoxy]phenyl]carbonyl]amino]-1-(4pyridinylmethyl)-4-piperidinecarboxamide (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(2pyridinylmethyl)-4-piperidinecarboxamide (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(3pyridinylmethyl)-4-piperidinecarboxamide (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(trans-3phenyl-2-propenyl)-4-piperidinecarboxamide (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-phenyl-4piperidinecarboxamide methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide (3R, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 - 1)]]]]quinolinyl)methoxy]phenyl]carbonyl]amino]-1-methyl-4piperidinecarboxamide

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- 45 (3R, 4S) -1- (dimethylcarbamyl) -N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide
- (3S, 4S) 1 hexyl N hydroxy 3 [[[4 [(2 methyl 4 (2 methyl50 quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide

(3S, 4S)-1-(2-fluoroethyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-

piperidinecarboxamide 5 (3S, 4S) - 1 - (2, 2 - difluoroethyl) - N - hydroxy - 3 - [[4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [[4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [[4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [[4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [[4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [[4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [[4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [[4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [[4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [[4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [[4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - 4 - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl) - (2 - methyl)] - N - hydroxy - 3 - [4 - (2 - methyl)] - N - hydroxy - (2 - methyl)] - N - hyquinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide 10 (3S, 4S) - N - hydroxy - 1 - (1 - methylpropyl) - 3 - [[[4 - [(2 - methyl - 4 - methylpropyl)]]]]quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide (3S, 4S) - 1 - (1-ethylpropyl) - N-hydroxy - 3 - [[[4-[(2-methyl - 4-15 quinolinyl)methoxy[phenyl]carbonyl]amino]-4piperidinecarboxamide (3S, 4S) - 1 - [1 - [[(1, 1-dimethylethyl)oxy]carbonyl] - 4 tetrahydropiperidinyl]-N-hydroxy-3-[[[4-[(2-methyl-4-20 quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy[phenyl]carbonyl]amino]-1-(4-25 tetrahydropiperidinyl)-4-piperidinecarboxamide (3S-4S)-1-[1-[(1,1-dimethylethyl)oxy]carbonyl]-3tetrahydropyrrolidinyl]-N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy[phenyl]carbonyl]amino]-4-30 piperidinecarboxamide (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(3tetrahydropyrrolidinyl)-4-piperidinecarboxamide 35 methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide 40 (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy[phenyl]carbonyl]amino]-1-(3thiophenylmethyl)-4-piperidinecarboxamide (3S, 4S) - N - hydroxy - 1 - (1 - methylethyl) - 3 - [[4 - (2 - methyl - 4 - methylethyl)] - 3 - [4 - (4 - methylethyl)] - 345 quinoliny1)methoxy]phenyl]carbonyl]amino]-1-oxo-4piperidinecarboxamide (3S, 4S) - N - hydroxy - 1 - (1 - methylethyl) - 3 - [[[4 - [(2 - methyl - 1 - oxo-4-quinoliny1)methoxy]pheny1]carbony1]amino]-4-50 piperidinecarboxamide

(3S, 4S) -N-hydroxy-1-(1-methylethyl)-3-[[[4-[(2-methyl-1-oxo-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-oxo-4-piperidinecarboxamide

- 5 (3S,4S)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-1-[2-(4-morpholinyl)-2-oxoethyl]-4-piperidinecarboxamide
- (3S,4S)-1-[2-(N,N-dimethylamino)-2-oxoethyl]-N-hydroxy-3[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide
- (3S, 4S)-1-(t-butylsulfonyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
- (3S, 4S)-1-(t-butylsulfonyl)-N-hydroxy-3-[[[4-[(2-methyl-1-oxo-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
 - (3S,4S)-1-(benzenesulfonyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
- 25
 (3S, 4S)-1-(t-butylsulfinyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
- 30 (3S, 4S) -N-hydroxy-1-(2-hydroxylethyl)-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
- (3S, 4S)-1-[2-[[[(1,1dimethylethyl)oxy]carbonyl]amino]ethyl]-N-hydroxy-3-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-4piperidinecarboxamide
- 40 (3S, 4S)-1-(2-aminoethyl)-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
- (3S, 4S)-1-[2-(N, N-dimethylamino)ethyl]-N-hydroxy-3-[[[4-[(2-45 methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide
- (3S,4S)-1-[(2S)-2-aminopropyl]-N-hydroxy-3-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide

WO 01/70673 PCT/US01/08334 (3S, 4S) - 1 - [(2R) - 2 - amino - 3 - hydroxypropy 1] - N - hydroxy - 3 - [[4 - amino - 3 - hydroxypropy 1] - N - hydroxy - 3 - [[4 - amino - 3 - hydroxypropy 1] - N - hydro[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-4-piperidinecarboxamide 5 (3S, 4S) - N - hydroxy - 3 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-[[(2R)-2pyrrolidinyl]methyl]-4-piperidinecarboxamide (3S, 4R) - N - hydroxy - 1 - (2 - hydroxylethyl) - 4 - [[[4 - [(2 - methyl - 4 - [[4 - [(2 - methyl - 4 - [(3 - methyl - 4 -10 quinolinyl)methoxy]phenyl]carbonyl]amino]-3piperidinecarboxamide (3S, 4R) - 1 - (2-aminoethyl) - N-hydroxy-4 - [[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-3-15 piperidinecarboxamide (3S, 4R)-1-cyclobutyl-N-hydroxy-4-[[[4-[(2-methyl-4quinoliny1) methoxy | phenyl | carbonyl | amino | -3piperidinecarboxamide 20 $(3R, 4R) - N - hydroxy - 4 - (\{4 - [(2 - methy] - (\{4 - [(2 - methy] - 4 - ([2 - methy] - (\{4 - [(2 - methy] - 4 - ([2 - methy] - (\{4 - [(2 - m$ quinolinyl)methoxylbenzoyl}amino)tetrahydro-2H-pyran-3carboxamide 25 (3S, 4S)-1-tert-butyl-N-hydroxy-3-({4-[(2-methyl-4quinolinyl)methoxy]benzoyl}amino)-4piperidinecarboxamide tert-butyl $2-[(3s, 4s)-4-[(hydroxyamino)carbonyl]-3-({4-[(2-$ 30 methyl-4-quinolinyl)methoxy]benzoyl}amino)piperidinyl]-2-methylpropanoate $2-[(3S,4S)-4-[(hydroxyamino)carbonyl]-3-({4-[(2-methyl-4$ quinoliny1) methoxy] benzoy1} amino) piperidiny1]-2-35 methylpropanoic acid methyl 2-[(3S,4S)-4-[(hydroxyamino)carbonyl]-3-({4-[(2methyl-4-quinolinyl)methoxylbenzoyl}amino)piperidinyl]-2-methylpropanoate 40 $(3S, 4S) - N - hydroxy - 3 - (\{4 - [(2 - methy] - 4 - [(2 - methy]$ quinolinyl)methoxy]benzoyl}amino)-1-[2-(4-morpholinyl)-2-oxoethyl]-4-piperidinecarboxamide 45 (3S, 4S)-1-[2-(dimethylamino)-2-oxoethyl]-N-hydroxy-3-($\{4$ -[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4-

piperidinecarboxamide

(3S,4S)-1-(1,1-dimethyl-2-propenyl)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4-piperidinecarboxamide

- 5 (3S,4S)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-tert-pentyl-4-piperidinecarboxamide
- (3S, 4S) -N-hydroxy-3-({4-[(2-methyl-4quinolinyl)methoxy]benzoyl}amino)-1-(2-propynyl)-4piperidinecarboxamide
- (3S,4S)-1-allyl-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4piperidinecarboxamide
 - (3S,4S)-N-hydroxy-1-(1-methyl-2-propynyl)-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4-piperidinecarboxamide
- 20
 (3S, 4S) -N-hydroxy-1-(1-methyl-2-propenyl) -3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-4piperidinecarboxamide
- 25 N-{(1R,2S)-4,5-dihydroxy-2-[(hydroxyamino)carbonyl]cyclohexyl}-4-[(2-methyl-4-quinolinyl)methoxy]benzamide
- (5S)-N-hydroxy-5-({4-[(2-methyl-4quinolinyl)methoxy]benzoyl}amino)-2-oxo-4piperidinecarboxamide
- (3S,4S)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-2-oxo-4-piperidinecarboxamide
 - (3S, 4S)-3-{[4-(2-butynyloxy)benzoyl]amino}-N-hydroxy-1-isopropyl-4-piperidinecarboxamide
- 40 (3S,4S)-3-{[4-(2-butynyloxy)benzoyl]amino}-N-hydroxy-4-piperidinecarboxamide
- tert-butyl (3S,4S)-4-[(hydroxyamino)carbonyl]-3-({4-[(2-methyl-3-pyridinyl)methoxy]benzoyl}amino)-1piperidinecarboxylate

WO 01/70673 PCT/US01/08334 $(3S, 4S) - N - hydroxy - 3 - ({4 - [(2 - methyl - 3 - m$ pyridinyl)methoxy]benzoyl}amino)-4piperidinecarboxamide 5 tert-butyl $(3S, 4S) - 3 - (\{4 - [(2, 5$ dimethylbenzyl)oxy]benzoyl}amino)-4-[(hydroxyamino)carbonyl]-1-piperidinecarboxylate $(3S, 4S) - 3 - (\{4 - [(2, 5 - dimethylbenzyl) oxy] benzoyl\}amino) - N -$ 10 hydroxy-4-piperidinecarboxamide (cis, cis) - 3 - Amino - 2 - [[[4 - [(2 - methyl - 4 quinolinyl)methoxy]phenyl]carbonyl]amino]-(Nhydroxy) cyclohexylcarboxamide -15 (cis, cis) -3-Methylamino-2-[[[4-[(2-methyl-4quinolinyl) methoxy] phenyl] carbonyl] amino] - (Nhydroxy) cyclohexylcarboxamide (cis, cis) -3-Dimethylmino-2-[[[4-[(2-methyl-4-20 quinolinyl)methoxy]phenyl]carbonyl]amino]-1-(Nhydroxy) cyclohexylcarboxamide (cis, trans) -3-Amino-2-[[[4-[(2-methyl-4-25 quinolinyl) methoxy] phenyl] carbonyl] amino] -1-(Nhydroxy) cyclohexylcarboxamide (cis, trans) -3-Dimethylmino-2-[[[4-[(2-methyl-4quinolinyl) methoxy] phenyl] carbonyl] amino] - (N-30 hydroxy) cyclohexylcarboxamide (cis, trans) - 3 - (1 - Methyl - 1 - ethylmino) - 2 - [[[4 - [(2 - Methyl - 4 - Methyl - 2 - [(3 - Methyl - 2 - Methyl - 3 - Methyl - 2 - Methyl - 3 - Methyl -

- (cis, trans) -3-(1-Methyl-1-ethylmino) -2-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino] (N-hydroxy)cyclohexylcarboxamide
- (cis, trans) -3-Methylamino-2-[[[4-[(2-methyl-4quinolinyl)methoxy]phenyl]carbonyl]amino]-(Nhydroxy)cyclohexylcarboxamide
- 40 (cis, cis) -3-Hydroxy-2-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]carbonyl]amino]-(N-hydroxy)cyclohexylcarboxamide

- N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-{[(2-methyl-45 4-quinolinyl)methyl]amino}benzamide
 - N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-{methyl[(2-methyl-4-quinolinyl)methyl]amino}benzamide

N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-(3-phenyl-4,5-dihydro-5-isoxazo[vl]benzamide N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[3-(4-5 pyridinyl)-4,5-dihydro-5-isoxazolyl]benzamide N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[3-(3pyridinyl)-4,5-dihydro-5~isoxazolyl]benzamide 10 N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[3-(2pyridinyl)-4,5-dihydro-5-isoxazolyl]benzamide N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[3-(4quinoliny1)-4,5-dihydro-5-isoxazoly1]benzamide 15 4-[3-(2,6-Dimethyl-4-pyridinyl)-4,5-dihydro-5-isoxazolyl]-N-{cis-2-[(hydroxyamino)carbonyl]cyclopentyl}benzamide N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-3-methoxy-4-20 [3-(4-pyridinyl)-4,5-dihydro-5-isoxazolyl]benzamide 3-Hydroxy-N-{cis-2-[(hydroxyamino)carbonyl]cyclopentyl}-4-[3-(4-pyridinyl)-4,5-dihydro-5-isoxazolyl]benzamide 25 N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[5-(2pyridinyl)-4,5-dihydro-3-isoxazolyl]benzamide N-{cis-2-[(Hydroxyamino)carbonyl]cyclopentyl}-4-[5-(4pyridinyl)-4,5-dihydro-3-isoxazolyl]benzamide 30 N-{4-[(hydroxyamino)carbonyl]-3-pyrrolidinyl}-1-[(2-methy]-4-quinolinyl)methyl]-1H-indole-5-carboxamide $N-\{2-[(hydroxyamino)carbonyl]cyclopentyl\}-1-[(2-methyl-4-$ 35 quinolinyl)methyl]-1H-indole-5-carboxamide N-hydroxy-3-({6-[(2-methyl-4-quinolinyl)methoxy]-1naphthoyl amino) - 4-piperidinecarboxamide N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-6-[(2-methyl-4-40 quinolinyl)methoxy]-1-naphthamide N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-6-[(2-methyl-4quinolinyl)methoxy]-2-naphthamide 45 N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-6-[(2-methyl-4quinolinyl)methoxy]-1,2,3,4-tetrahydro-1isoquinolinecarboxamide

N-{2-[(hydroxyamino)carbonyl]cyclopentyl}-1-[(2-methyl-4-quinolinyl)methyl]-1H-benzimidazole-5-carboxamide

 $N-\{2-[(hydroxyamino)carbonyl]cyclopentyl\}-1-[(2-methyl-4-quinolinyl)methyl]-1H-indole-4-carboxamide$

- 5 (±)-cis-N-hydroxy-2-[[4-[(2-methyl-4quinolinyl)methoxy]benzoyl]amino]-1cycloheptanecarboxamide
- (4S, 5R) -N-hydroxy-5-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-2-oxohexahydro-1H-azepine-4-carboxamide
- (3S,4S)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-7-oxohexahydro-1H-azepine-4-carboxamide
 - (3S, 4R)-N-hydroxy-4-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-7-oxohexahydro-1H-azepine-3-carboxamide
- 25 (4S,5R)-N-hydroxy-5-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-7-oxohexahydro-1H-azepine-4-carboxamide
- (2S,3R)-N-hydroxy-3-({4-[(2-methyl-4quinolinyl)methoxy]benzoyl}amino)-2pyrrolidinecarboxamide
- (2R,3R)-N-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-2pyrrolidinecarboxamide, and

- tert-butyl (2S,3R)-2-[(hydroxyamino)carbonyl]-3-({4-[(2methyl-4-quinolinyl)methoxy]benzoyl}amino)-1pyrrolidinecarboxylate
- or a pharmaceutically acceptable salt form thereof.
- 8. A pharmaceutical composition, comprising: a
 45 pharmaceutically acceptable carrier and a therapeutically
 effective amount of a compound according to one of Claims 1,
 2, 3, 4, 5, 6, or 7 or a pharmaceutically acceptable salt
 form thereof.

9. A method of treating a condition or disease mediated by MMPs, TNF, aggrecanase, or a combination thereof in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound according to one of Claims 1, 2, 3, 4, 5, 6, or 7 or a pharmaceutically acceptable salt form thereof.

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10. A method of treating according to Claim 9, wherein the disease or condition is referred to as acute infection, acute phase response, age related macular degeneration, alcoholism, anorexia, asthma, autoimmune disease, autoimmune 15 hepatitis, Bechet's disease, cachexia, calcium pyrophosphate dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary disease, coagulation, congestive heart failure, corneal ulceration, Crohn's disease, enteropathic arthropathy, Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid withdrawal syndrome, gout, graft versus host disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation, intermittent hydrarthrosis, Lyme disease, 25 meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease, periodontitis, polymyositis/dermatomyositis, post-ischaemic reperfusion injury, post-radiation asthenia, psoriasis, psoriatic 30 arthritis, pydoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and tumor invasion by secondary metastases,

spondylitis, stroke, systemic lupus erythematosus,

WO 01/70673 PCT/US01/08334 ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis.

- 5 11. A Compound according to one of Claims 1, 2, 3, 4, 5, 6, or 7 or a pharmaceutically acceptable salt form thereof for use in therapy.
- 12. Use of a compound according to one of Claims 1, 2, 3, 4, 5, 6, or 7 or a pharmaceutically acceptable salt form thereof for the manufacture of a medicament for the treatment of a condition or disease mediated by MMPs, TNF, aggrecanase, or a combination thereof.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



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(54) Title: CYCLIC β-AMINO ACID DERIVATIVES AS INHIBITORS OF MATRIX METALLOPROTEASES AND TNF-α

(57) Abstract: The present application describes novel cyclic β -amino acid derivatives of formula (1) or pharmaceutically acceptable salt forms thereof, wherein ring B is a 5-7 membered cyclic system containing from 0-2 heteroatoms selected from O. N, NR³, and $S(O)_p$, and 0-1 carbonyl groups and the other variables are defined in the present specification, which are useful as metalloprotease and as TNF- α inhibitors.

INTERNATIONAL SEARCH REPORT

Intes .onal Application No PCT/US 01/08334

A. CLASSIF IPC 7	FICATION OF SUBJECT MATTER C07D401/12 C07D405/12 C07D307 A61P29/00 C07C259/08	/24 CO7D215/14 A61K	(31/55		
According to	International Patent Classification (IPC) or to both national classification	cation and IPC	······································		
B. FIELDS	SEARCHED currentation searched (classification system followed by classification system followed by classifi	lion symbols)			
IPC 7	CO7C CO7D A61K A61P	·			
Documentat	ion searched other than minimum documentation to the extent that	such documents are included in the fields s	searched		
Electronic d	ata base consulted during the international search (name of data b	ase and, where practical, search terms use	d)		
EPO-In	ternal, WPI Data, CHEM ABS Data				
C. DOCUMI	ENTS CONSIDERED TO BE RELEVANT				
Category *	Citation of document, with indication, where appropriate, of the re	elevant passages	Relevant to claim No.		
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		-/			
X Furt	ther documents are listed in the continuation of box C.	Patent family members are listed	d in annex.		
"A" docume consider filing of the citatio "O" docume other "P" docume othe	ategories of cited documents: ent defining the general state of the art which is not dered to be of particular relevance document but published on or after the international date ent which may throw doubts on priority claim(s) or is cited to establish the publication date of another in or other special reason (as specified) ent reterring to an oral disclosure, use. exhibition or means ent published prior to the international filling date but han the priority date claimed	"T" later document published after the int or priority date and not in conflict will cited to understand the principle or II invention "X" document of particular relevance; the cannot be considered novel or cannot involve an inventive step when the d' "Y" document of particular relevance; the cannot be considered to involve an in document is combined with one or ments, such combination being obvidin the art. "3" document member of the same paten	h the application but heavy underlying the claimed invention of the considered to occurrent is taken alone claimed invention inventive step when the lore other such docupous to a person skilled		
_	actual completion of the international search	Date of mailing of the international se			
1	5 November 2001	30/11/2001	,		
Name and	mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Diederen, J			

INTERNATIONAL SEARCH REPORT

Inte. Ional Application No PCT/US 01/08334

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	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	 Relevant to als:- */-		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	 Relevant to claim No.		
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3 (partially), 5 (partially), 8-12 (partially)

Present claims 1-3, 5 and 8-12 relate to an extremely large number of possible compounds, compositions, methods and uses. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds, compositions, methods and uses claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely the compounds of claims 4 and 6 and the corresponding compositions, and uses thereof.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. onal Application No PCT/US 01/08334

					,	
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